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THREE LECTURES

ON

UNICELLULA CANCRI

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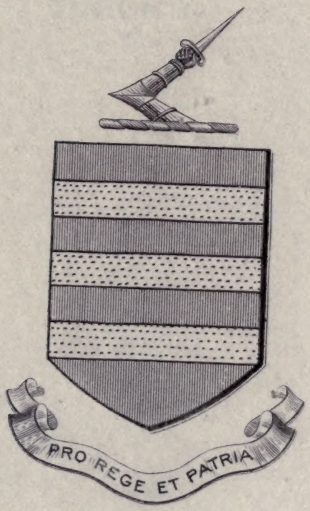

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THREE LECTURES ON UNICELLULA CANCRI

THE PARASITE OF CANCER

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THREE LECTURES ON UNICELLULA CANCRI

THE PARASITE OF CANCER

BY THE LATE

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PREFACE

Owing to the death of the late Sir Henry Butlin, the author of these lectures, their final preparation for publication in book form has had to be relegated to other hands. The first two were prepared for delivery before the Royal College of Surgeons in November of last year, being the Hunterian Lectures which Sir Henry had intended to give in virtue of his office of a Hunterian Professor for the year. Unhappily, as the time appointed drew near, the author found that, owing to his increasing weakness, he could not deliver them himself. Under these circumstances Sir Henry did me the honour of asking me to read them ; and my having done so is the reason of the further request by Mr. Furnivall that I should edit this volume, for Sir Henry left instructions that such publication should be undertaken.

The first two lectures, which were published in the *British Medical Journal* shortly after their reading, are here preceded by an intro-

duction; to Lecture II. is added an appendix; and they are concluded by a third lecture, also published at the suggestion of Mr. Furnivall in the *British Medical Journal* recently, the subject-matter of which was only excluded from the others by the time limit.

In the publication but few and unimportant changes have been made. I felt it incumbent on me to leave as much unaltered as possible; and in spite of the rapid course of the author's illness, during which time the additional parts were written, these are remarkably clear and in good order. From the introduction alone, which was written last, I have deleted sentences, which added nothing to the subject, and which I thought, had Sir Henry been able to ponder them, he would himself have struck out.

I have to thank Mr. Furnivall for much kindness and advice in the matter.

R. H. PARAMORE.

May 1912.

INTRODUCTION

In the course of last summer (1911) I asked the Council of the Royal College of Surgeons for permission to deliver two unofficial lectures on Cancer in the Theatre of the College in the course of the following autumn or winter. I did not apply for any of the official lectures, because I did not wish to displace lecturers who might have more valuable information to impart. But my colleagues preferred I should be appointed a Hunterian professor to the College and deliver my two lectures as one of the Hunterian Professors of the year. I need scarcely say that I was very proud to abide by their decision, and the lectures were delivered on November 13 and 15.* As it was impossible to compress all I had in mind within the limits of the lectures assigned to me, I did not

* As I was suffering from laryngitis and loss of voice, I was not able to deliver the lectures myself: I was present, and very much gratified by the manner in which they were read by Dr. R. H. Paramore.

attempt to deal with *all* the known phenomena of cancer. I only lightly touched on the question: "Where does the cancer cell come from?" and I did not discuss the question of the influence which the adoption of my theory must necessarily have on our working views ("working theory") of cancer.

With regard to the origin of the cancer cell, I have nothing to add to what is said in Lecture II. It is beyond the scope of my lectures. I maintain only that the cancer cell is an independent species of organism—an absolutely new species—consisting of a single cell. It is so from the moment it is recognisable as the cancer cell, and it remains so to the death of the cancer cell. The first place in which it is recognised is in the tissues of the host. It is not any part of my business to explain how it comes to be there, or how it has become an independent creature. I have spoken of it as a new creation; but how and when the creation takes place, I do not know. And I should not have referred to its origin in my lectures, had it been possible to omit it. But this question has been so much before the minds of cancer investigators that it was not possible to pass it over without notice. I therefore contented myself with mentioning

the two chief theories which prevail regarding the origin of the cancer cell, and with pointing out that the evidence in favour of one of those theories is much stronger than the evidence in favour of the other theory, and that scientific opinion accepts the evidence, so far as it goes, in favour of formation (or creation) of the cancer cell within the body of the host. I express no opinion on the matter, particularly as it is possible that other theories of the origin of the cancer cell may yet be put forward.

I shall not discuss the theories which have been put forward in the course of the last few years to account for the improprieties and curious conduct of the cancer cell. Some of them are mentioned in the second lecture. Professor Calkins has dealt with them very skilfully in the *Journal of Experimental Medicine* (Vol. X. p. 283, 1908, "On the so-called Rhythms of Growing Energy in Mouse Cancer"). Curiously enough, he himself has drifted back to the external parasite theory. For, after all, his self-contained and ordinarily invisible micro-organism, living in symbiosis with the cell, can only be a cell-parasite. The excuse for it seems to be that it is so small that nobody can see it, and that it is a gentle-natured creature, and lives on good terms with

the cell which is its host. A parasite of external origin, whether small or large, whether benign or malign, whether it be animal or vegetable, will not explain the phenomena of cancer as they occur in man and animals, and that is the reason why a large number of investigators, including the clinical pathologists, have abandoned the search for it.

As my strength is rapidly drawing to a close, I may not be able to speak of all the phenomena of cancer in relation to my theory. They are not many, and are for the most part quite subordinate.

I have to thank Dr. Bashford for his interest in the preparation of my drawings and diagrams. They were executed by Mr. Ford, that most able microscopic artist, under the supervision of Dr. Bashford. Some of them are from sources which are acknowledged, the others are from my own sections.

THREE LECTURES ON UNICELLULA CANCRI

THE PARASITE OF CANCER

LECTURE I

In the Bradshaw Lecture of November 1905, I put forward the proposition that "the carcinoma cell is an independent organism like many a protozoon; that it lives a life which is wholly independent and proper to itself; and that it lives as a parasite in the body of the animal which is affected with carcinoma, deriving its nourishment from this host, and doing nothing to repay the host for the sustenance of which it robs him." * Until shortly before I delivered the lecture, I thought that I was the first person to suggest that the cancer cell is itself the parasite of cancer, but I found that Hauser had done so in 1903.† And

* *B. M. J.*, 1905, II. 1566.

† Ziegler's *Beiträge z. Path. Anat.*, XXXIII., S. 1, 1903.

a couple of years ago Dr. Powell White showed me that he had done so in the Erasmus Wilson Lectures at the Royal College of Surgeons as long ago as 1902.* But I think that neither White nor Hauser had carried the matter to its logical conclusion, so far as to insist that the cancer cell is a new organism—a new creation of animal being—not a mere changed cell.†

So far as I know, then, I stood alone in the belief that the cell of carcinoma is a new creation of living beings, consisting of a single cell, and governed by natural laws just as clear and just as defined as those which govern single-cell organisms which are recognised by naturalists. In 1905 I maintained this view only for the cells of carcinoma. For the last five years and more, the matter has been constantly before my mind. A great deal of new information and material has been provided during that period, and I am able now to

* *Lancet*, 1902, I.

† "All the phenomena of malignant and other tumours can be explained on other grounds, viz. on the view that the cells take on an independent mode of growth, and behave as parasites themselves."

"Once the cells have acquired this habit (Adami's Habit of Growth), they behave as independent parasites." (White, *l.c.*)

maintain the view, not only for carcinoma, but for every variety of malignant disease.

I am quite aware that my ignorance of Biology and of the lowest forms of animal life may render my attempt ridiculous in the eyes of naturalists. And I should never have ventured to undertake the task had there been any person particularly fitted for it, and willing to accept it. A wide grasp of three kinds of knowledge is required :

A knowledge of the Protozoa ;

Experience of experimental investigation of cancer ;

And experience of the clinical pathology of cancer in the human subject.

I do not know any one person who combines these three kinds of knowledge in himself. There is only one distinguished protozoologist, so far as I know, who is engaged in investigation of cancer—Professor Calkins, of the Columbia University of New York—and he is not a medical man. And it is, I am sorry to say, notorious that the masters of experimental investigation are, for the most part, very ignorant of the clinical pathology of cancer ; while it is equally true that the physicians and surgeons who have studied cancer from the clinical and microscopical

aspects, are not acquainted with protozoology or with experimental investigation.

The class to which I have the honour to belong—the Clinical Pathologists—is looked down upon by the other two classes, and I have been told that its day is past. But I claim a right to present my theory on the ground that I have spent a great deal of time in the course of many years in the study of the clinical pathology of cancer, and that I have been closely observant of the actual work of the Imperial Cancer Research since its foundation, have constantly associated with the staff, and have been a member of the publication committee of all the scientific reports which have been published by the Research. On the other hand, I am wholly dependent for my statements on the life-history of the Protozoa on the works of Calkins and Doflein, and the references which I have found in them, and to some pretty sharp criticism of my views in a letter which Professor Calkins was kind enough to write me.

I shall divide the subject into two parts. In the first part I shall endeavour to show that there is no essential difference between cancer cells and certain other parasites in their relation to their host. In the second part I

shall show that almost all the phenomena of cancer with which I am acquainted can be readily explained on this theory.

The parasites of which I am going to speak are the Protozoa; I am not going to speak of such micro-organisms as bacilli and bacteria. I use the Protozoa, not because I intend to insist that the cancer cells must be included amongst the Protozoa, but because they most closely resemble the Protozoa in their relation to the body of the host, and perhaps in their mutual relations.

Certain of the Protozoa appear only to live as parasites, whilst others of them are never parasitic, and others again are able to exist either as parasites or external to the body of any host. The powers of the parasites are strangely and strictly defined. Doflein (of whose work I am going to make very free use) * says: "When a protozoon gets into another organism, there begins at once a fight between the two, which ends in an easy victory of the larger, many-celled beast if the protozoon is not a parasite, and if the many-celled beast enjoys its normal natural resistance. But if the protozoon is fitted for parasitism, then the

* *Lehrbuch der Protozoenkunde*, Jena, 1909.

fight is in earnest. And in this fight that organism conquers which is able to overcome the other with its fighting weapons." * But it is quite certain that every parasitic protozoon which finds its suitable host does not succeed in holding its own against the resistance of the host.

Many groups of parasites are limited to certain groups of hosts—the Sarcosporidiidæ, for instance, to air-breathing vertebrates, whilst the Gregarinidæ have not been found in vertebrate hosts.† But the limitations are much more strict than this. For, of the same species of parasite, different varieties are found in different varieties of a species of host. Thus the Sarcosporidiidæ, which are believed to be exclusively found in mammals,‡ and which have been found in horses, cows, buffaloes, mice, rats, man, etc., do not all occur equally and at random in all these animals, but certain varieties of the Sarcosporidiidæ occur only in certain varieties of mammal. *Sarcocystis miescheriana* inhabits the body of the pig ; *Sarcocystis tenella* loves the sheep ; while *Sarcocystis muris* is a parasite of the house-mouse and the rat. And those varieties of parasite which are particular to certain varieties of mammal, as the *Babesia*

* Doflein, p. 276. † *Ibid.*, p. 263. ‡ *Ibid.*, p. 805.

bigemina is to cattle, cannot be implanted in other mammals. Experiments which have been made on rats, guinea-pigs, sheep, and pigeons have always failed.* On the other hand, there are parasites which can exist in several or many varieties of host, yet even these exhibit strange powers of selection. Thus, *Trypanosoma Brucei* and *Trypanosoma Lewisi* can breed in dogs, in the blood of the same animal, but if they are injected from this blood into rats, *Trypanosoma Brucei* disappears, and only *Trypanosoma Lewisi* lives and thrives.†

Just as particular varieties of Protozoa are limited to particular varieties of host, so they are often limited in like manner to particular parts of the bodies of their hosts. Thus, the Sarcosporidiidæ are parasites of muscles; Trypanosoma is a blood parasite; the Coccidiidæ are parasites of cells, particularly of epithelial cells.‡ But they exhibit powers of selection much more marked than this. *Myxobolus Cyprini* is a parasite of the kidney-epithelium of the carp. The Sarcosporidiidæ not only affect the muscles, but most of the varieties affect particular muscles or groups of muscles. Thus, *Sarcocystis miescheriana* takes to the muscles of the larynx, to the

* Doflein, p. 274. † *Ibid.*, p. 264. ‡ *Ibid.*, p. 264.

diaphragm, and intercostal muscles; *Sarcocystis muris* affects the muscles of the trunk. And, although several varieties of Sarcosporidiidæ are chiefly found in the muscles in the neighbourhood of the alimentary canal, which they may have easily reached from the mouth or œsophagus, others of them are found in muscles far distant from the alimentary canal, such as the intercostal muscles, or the muscles of the trunk. Other parasites, again, appear to be equally at home in several or many tissues of the host. *Nosema bombycis* (which produces the Pébrine disease of the silkworm) occurs in the intestine, the fat-bodies, the sexual organs—in short, in all the organs of the *Bombyx mori*.

Far more remarkable and interesting than this power of selection, is the generalisation which may take place of parasites which are usually limited to a single structure of the host. Thus, *Myxobolus Pfeifferi*, which is usually a harmless parasite in the kidney of the barbel, makes terrible havoc of the same fish in the water of certain rivers (the Seine, the Marne, the Maas, the Rhine and Mosel), where it attacks almost all the organs of the body of the fish—the connective tissue of the intestine, the kidney, the spleen, the liver,

FIG. 1.—Barbel suffering from *Barbenseuche*; tumours formed by *Myxobolus* (after Doflein). *Protozoenkunde*, II Aufl., Jena, 1909, Fig. 730.

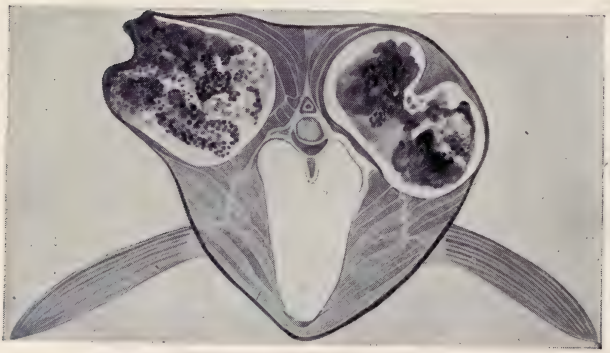

FIG. 2.—Section of a barbel, showing symmetrical tumours, that on the left side ulcerated (Doflein, Fig. 731).

but, above all, the muscular system, in which it forms great lumps and tumours, which stand out on the surface of the animal, and are quite characteristic of the barbel-sickness (*Barbenseuche*)* (Figs. 1 and 2.)

It is possible that the Protozoa, which are parasitic—that some of them, at least—take an active part in their migration within the host. But they are also carried in the blood and lymph to the organs and tissues in which they are generalised. Thus, *Isospora Lieberkühni* (a parasite of the frog) first attacks the epithelium of the intestine, then penetrates into the vessels of the mucous membrane, and is carried by the blood to the lungs, liver, spleen, and other parts. *Entamœba histolyca*, the parasite of Dysentery, makes its way through the walls of the rectum, and is supposed to be conveyed through the ductus choledochus into the liver. *Lymphosporidium Calkins* (which produces severe epidemics in fish) appears in the form of small amœboid bodies in the lymph, attacks the muscles of the intestines and other organs, passes again into the lymph in its developed form, and produces numerous spores, which are conveyed to all parts of the body.

* Doflein, p. 776.

It is interesting to observe the changes which take place in many of the Protozoa, either to adapt them to parasitism or to altered conditions of life in the bodies of different hosts. Thus, the Trypanosoma will vary in size, in the situation of its nucleus, etc., according to the medium in which it lives. *Trypanosoma Lewisi* loses its undulating membrane in certain artificial cultures, and the Sarcosporidiidæ are not constant in form, for the cells, closely packed together during their development, mutually deform one another.*

Although some of the parasites are able to take formed nourishment, most of them, and all the cell parasites, live by osmosis.† The Sporozoa, for instance, live exclusively by the osmotic taking of fluid nourishment.‡ Many of them perish with their host; for even if they escape from the dead body of the host, they may be unable to exist outside the body of a host. But they often exhibit a marked tenacity of life; for they may live for days after the death of the host and of every tissue and cell of the host.

With regard to the liability of parasitic Protozoa to death, it is held by Weismann and his school that the Protozoa are immortal, in the

* Doflein, p. 805. † *Ibid.*, p. 264. ‡ *Ibid.*, p. 613

sense that the young animals are in part composed of the substance of the parent. As a matter of fact, they undergo degeneration, are liable to disease, fade, waste, and die like other living creatures. And they are often killed by the invasion of their bodies by micro-organisms, the Bacteria, which are then parasites of parasites. I must ask you to bear this in mind when we come to consider the cells of cancer presently.*

Of liability of animals of the same species to a particular parasite, the evidence goes to prove that some individuals of a species are immune to the attack of a parasite, other individuals recover from the attack of a parasite, while other individuals again suffer badly from it, or die. Take, as an example, the Hæmoglobinuria of cattle (Texas fever), which is attributed to *Babesia bigemina*, a parasite which is not directly transferred from cow to cow, but is introduced into the cattle by a beetle (*Boophilus annulatus*).† Whole herds are attacked in the plains of Texas. But all the animals do not show symptoms of the disease, and some of those which are attacked recover. Pigniéres gives an account of a herd of 1,000 adult cattle and 450 calves. Of the

* Doflein, p. 280. † *Ibid.*, p. 752.

adults, 630 died—an enormous mortality—but only 10 of the 450 calves perished of the disease. Calves, if they suffer at all, suffer mildly. There is generally no hæmoglobinuria, and at the end of a fortnight they are often quite recovered. Nevertheless, the Babesia may still be found in the blood of these recovered calves, so that they appear to have acquired immunity against the poison of the parasite. Whether they can be artificially immunised by the injection of the blood of beasts which have been cured of the disease has not yet been clearly ascertained.

It appears probable that the body of the host contains, or may produce, on demand, a substance dangerous to the life of the parasite which is in it. Of this the parasite may die. But if it can withstand the dangerous substance, it seems to gain greater strength. It has acquired immunity by its successful resistance to the dangerous substance, and may flourish more actively than before. But the activity of a parasite is probably not always the same. For, as they show alternate periods of activity and depression in cultures, eating more, growing faster, multiplying abundantly at one time, and displaying sluggard qualities at another (Actinosphæria,

Infusoria, etc.), so it is probable they are subject to similar periods of activity and depression in the body of the host.* Whether, during these periods of depression, they are devoured alive by phagocytes, I do not know, but their dead bodies appear to be eaten by phagocytes.† The effect of parasites on their hosts depends largely on whether they produce toxines dangerous to the host or not. Many of them (such as the parasite of Malaria) are toxic. And these are naturally much more dangerous to the host than the non-toxic parasites. But their virulence varies, like their vital activity; they are seldom or never so actively virulent as the bacteria and bacilli, and take much longer to produce serious or fatal illness in the host.

The non-toxic parasites are much less dangerous to life. They are often unperceived —are mere "commensales." But they may destroy the cells and tissues which they attack to such an extent as to produce serious effects upon the health of the host. They may destroy the host by enormous increase in numbers, and particularly by interfering with the working of vital organs. I have already mentioned the barbel-sickness, which is so fatal to the fish in France and Germany. The tumours

* Doflein, p. 238. † *Ibid.*, p. 276.

sometimes ulcerate. The Coccidiidæ appear to produce their effects by destruction of the tissues they invade. *Eimeria Stiedæ*—a common coccidium of the rabbit—causes the formation of tumours which may grow as large as a hazel-nut, and contain fluid, in which are found quantities of epithelial cells and coccidia.* *Lymphosporidium Calkins* (a parasite of fish to which I have already referred) is apt to fill the lymph-vessels so full that serious disturbance, the formation of ulcers, and death result from the stoppage of the flow of lymph.† *Sarcocystis tenella* sometimes chokes sheep by producing great sarcosporidian tumours in the neighbourhood of the air passages.‡

It seems probable that some parasites are capable of existing during long periods of time, even when they are not living their usual life, in the sense that a parasite which is, under ordinary circumstances, toxic to the host, may cease to be toxic, yet still exist. Thus, *Babesia bigemina* is often found in the blood of calves which have long recovered from the disease which it produces. It is well known that human beings who have contracted malaria may recover from it and may live for years

* Doflein, p. 630. † *Ibid.*, p. 821. ‡ *Ibid.*, p. 811.

without an attack, and then may be suddenly and unexpectedly attacked, even when they have been living meanwhile in non-malarial regions. It is evident the parasite is living in the body of the host during this long period, but it is almost equally evident that it just maintains its existence, and has lost its activity in face of the increased resistance of the host.

It will be noticed that I have used the term " power of selection " in speaking of the predilection of particular parasites for particular species of animals, for particular varieties of those species, and for particular organs and tissues of their hosts. The only reasonable explanation of these predilections is that the parasite finds the nourishment suitable to it in the particular host and parts of the host which it infests, or encounters less resistance there. *Eimeria Stiedæ*, for instance, which is contained in the grass on which many animals are feeding, must have an opportunity of entering the alimentary canal of cows, of horses, of sheep, and other animals. And undoubtedly it does enter it. But the only one of the animals which feed on the grass in which they are so abundant, which harbours and nourishes the parasite, is the rabbit. The waters which contain *Myxobolus Pfeifferi* also contain

Myxobolus Cyprini and *Myxobolus Neurobius*, and all kinds of fish which inhabit these waters must swallow myriads of all three varieties of parasite. But only the one particular parasite thrives in the one particular variety of fish which it affects. I would keep constantly before your minds this explanation of the power of selection of parasitic Protozoa.

Before leaving the parasitic Protozoa, two characters which they have in common should be referred to. First, whatever office the parasite may serve—whatever effect it may produce on the host—it, for its own part, has only two objects in view, if such an expression is permitted in speaking of so lowly a creature. It strives to live and to reproduce—to maintain the individual and to continue the species. If, in a suitable host, it does not succeed in reaching a suitable part of the body within a reasonable period, it will die, and the species will cease to exist in that host. The rapidity and completeness of its destruction will depend on many circumstances, but the general statement is correct.

Second, it breeds true. The young animals are always of the same species as the animals from which they were derived. I believe some doubt has been expressed whether Hæmo-

sporidiidæ may not be derived from Flagellidia.* I am not competent to speak on this, but it may be stated quite certainly that Sporozoa are not bred from Rhizopoda or Rhizopoda from Ciliata, that *Sarcocystis miescheriana* does not become *Sarcocystis muris*, and that *Nosema bombycis* never produces *Nosema destruens*, or the reverse.†

I now come to the comparison between the cancer cell and the parasitic Protozoa in their life-history and their relation to the host ; and I propose to treat it in the reverse order, taking the individual cells first, and dealing with the characters which they have in common afterwards.

First, I must premise that there is no one cell for every kind of malignant disease, nor is there one cell for the carcinomata and another cell for the sarcomata. Every variety of malignant tumour has its own typical cell, and the characters, the selection of locality, and relations of each variety of cancer cell to the host are sharply defined, and differ as

* Doflein, p. 739.

† There are other properties on which I must not touch, such as the periodicity which some of the Protozoa exhibit in relation to their vitality. Time will not permit me to do so. (Calkin's *Protozoology*, 1909, p. 106.)

widely as, though not more widely than, those of the varieties of Protozoa which belong to the same species.

Take first the cells which resemble the cells of the deeper layers of the epidermis, or of the appendages of the skin. They are very regular in size and shape, and are collected in masses in spaces of the connective tissue, usually of the skin or subcutaneous tissue. The external cells of the group are often modified in shape, and tend to become cubical or even columnar. They seem to have no power of establishing themselves in distant tissues and organs. On the other hand, their tenacity of life in and around the part in which they first appeared is little less than marvellous (Fig. 3).

Next, take the squamous cells. They resemble the cells of the epithelium of the skin, but are not so regular in size and shape, and the nuclei are large—out of proportion to the size of the cell. They form masses, which sometimes recall the natural dipping of the epithelium between the papillæ, but often seem to be massed together with no further design than to find sitting, or even standing room. And in this attempt they are often squeezed in such a manner (Fig. 4) that they

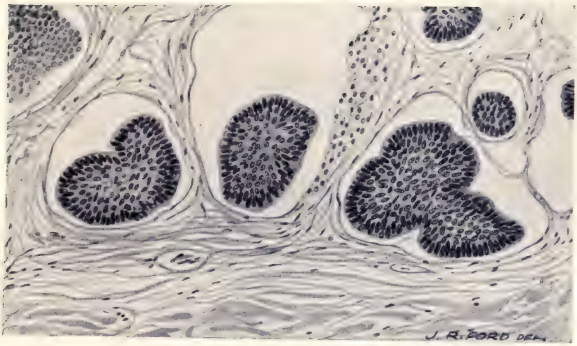

FIG. 3.—Cells of a rodent ulcer. The masses have separated from the walls of the cavities in which they lie.

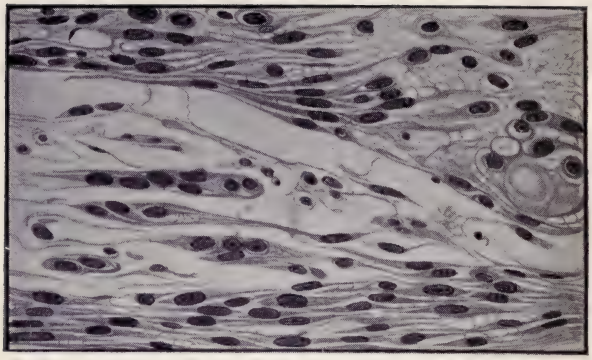

FIG. 4.—Squamous carcinoma of tongue, the cells of which are elongated like spindle-cells.

FIG. 5.—Metastatic tumour of thyroid cancer (borrowed).

may be elongated, and look more like spindle cells than squamous cells. They extend into the spaces between the muscular fibres as they grow beneath the surface, forming columns of cells which are easily distinguishable. Whenever they are in close and easy relation with the lymphatic glands, it may be accepted as a rule to which there are few exceptions, that they will find their way into those glands, and will grow and multiply there.

Now, consider the cells of Spheroidal type (Figs. 5 and 13; also Figs. 15 and 16). They collect in spaces of the connective tissue, sometimes in such a manner as to recall the structure of the gland whose epithelium they pattern (Fig. 5). They spread along the lymphatic channels, and are conveyed into the lymphatic glands, where they are well received and flourish. They are conveyed by the blood into other organs. They can live and multiply in many organs. But they select, by preference, the liver and lungs, and the medullary tissue of the bones, particularly of the femur and vertebræ of the lumbar region, just as certain Sarcosporidiidæ have a liking, not merely for muscles, but for certain muscles or groups of muscles. They exhibit a wonderful tenacity of life, for, after lying dormant for many

years—as many as nine or ten, or more—they may suddenly thrive and multiply, and produce large masses of their like in the space of a few weeks or months. Although they are probably chiefly conveyed to different regions of the body in the form of single young cells, it is also well known that masses of them grow into the interior of blood and lymphatic vessels,* and that emboli of them may be carried into parts which are favourable to their reception. It is also known that many of them perish in their journeying. They may be found in blood-vessels and in the thoracic duct in a condition of degeneration and decay (Fig. 6).

One of the most interesting and favourable objects of study is the columnar or cylindrical cell (Fig. 7). It resembles the cells of the columnar glands of the alimentary tract. Its tendency is to arrange itself in the same fashion as the columnar cells are arranged in the glands of the stomach and intestine, sometimes so precisely that it is difficult to believe that the section of the carcinoma is not a section of normal glands. But the imitation is usually much coarser, and there

* Goldmann, *Studien zur Biologie der Bösartigen Neubildungen.* Tübingen, 1911.

FIG. 6.—Degenerated cancer cells in an organised thrombus in a blood-vessel (after Martin B. Schmidt). *Die Verbreitungswege der Karzinome*, Jena, 1903, Plate, Fig. 3.

FIG. 7.—Columnar-celled cancer of the rectum (after Cripps). *Diseases of the Rectum and Anus*, 1884, Pl. VI.

FIG. 8.—Giant and spindle-celled sarcoma. *Path.-Trans.* vol. xxxi., 1880, Pl. XVII.

is evidence of slovenly work in the characters and disposition of the cells. As in the previous case, the cell makes its way into the surrounding and subjacent tissues, into the lymphatics and lymphatic glands, and is there speedily at home. It also has a great fancy for the liver, and in a less degree for the lung, and it now and then grows in the medullary tissue of one of the long bones —the humerus, for example, or such a flat bone as the ilium.

Now, consider the group of spindle cells (Fig. 8). They are elongated, tapering at each end. They vary much in size, and their form is often modified by pressure. But the general form is maintained wherever the cells occur. They spread widely in the surrounding tissues. It must be a very wide removal which is to get rid of them. They travel in the blood and in the lymph, so far as we can judge, but although they may thrive in the interior of lymphatic glands, the glands are often free from them. On the other hand, they have a great liking for the lungs—perhaps more than for any other part. They multiply in the lungs so rapidly as to produce large and numerous masses in them, and that is a frequent cause of the death of the host. These spindle cells

are for the most part very strong and vigorous, grow quickly and multiply abundantly, and find subsistence in many organs.

There is another variety of spindle cell, which multiplies to form tumours. The cells are often of small size, and the outline of the cell may be so faint and the nucleus so distinct that some of them have been called "fibro-nucleated." * These cells are endowed with very limited powers. They spread into the surrounding parts; in these parts they will live and thrive. But they appear quite unable to effect a successful attack upon any distant part, for they are not met with in the neighbouring glands, or in the liver, or lungs, or bones, or elsewhere. It is no excuse to say that their form and size are not favourable to transference by the blood and lymph. They are small and of convenient shape for transfer, much more so than many large spindle cells which are readily conveyed both by the blood and lymph.

Of the round cells (Fig. 9), it may generally be said that it is very difficult to distinguish them from the cells of the masses which make up the infective tumours. Indeed, it is often

* Paget, *Lectures on Surgical Pathology*, 1853, vol. ii., p. 155.

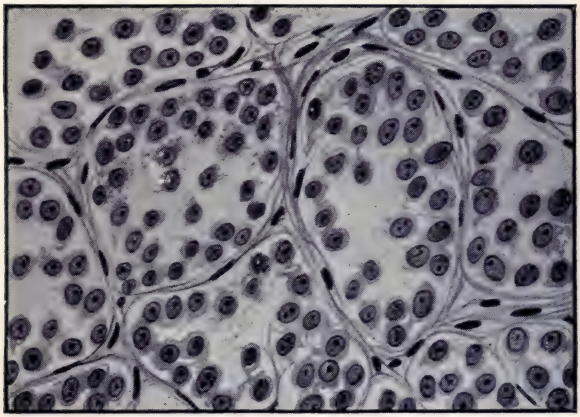

FIG. 9.—Large round-celled sarcoma of the testis of a boy: the cells are much larger and more distinct than usual.

impossible to do so by their anatomical characters. For the most part, it may be affirmed that they possess a remarkable vitality, not exceeded (seldom equalled) by any other cancer cell. They multiply rapidly—so rapidly that in some cases they produce immense masses in a few weeks, and the growth of the mass may be associated with symptoms of general fever. They seem much less influenced by the resistance of the host, or much more capable of finding nourishment, or less dependent on a very special diet, than most other cancer cells. For they seem very little limited to particular organs and tissues compared with most other varieties of cell. They flourish in the lymphatic glands, if they reach them, in the bones, skin and subcutaneous tissue, kidneys, liver, lungs—indeed, like *Nosema bombycis*, almost everywhere. I believe they would spread all over the body, if the host were not destroyed by them before they have had the opportunity to do so.

There is one variety of cell which I must not pass over without notice—the "giant cell" (Fig. 8). These cells only form a certain proportion of the masses in which they occur—less than one-half—and the remainder of the mass is composed usually of spindle cells.

Having regard to their size alone, it is not surprising that giant cells travel with difficulty in the blood and lymph. It would be expected that the spindle cells of which the mass is chiefly formed might travel and establish themselves in other places. But it is notorious that they seldom do so.

These examples will suffice to illustrate some of the resemblances of the life-history of the cancer cells to the parasitic Protozoa. It will be seen that they are as careful in the selection of locality as are the varieties of parasitic Protozoa. They spread in the interstices of the tissues in which they first appear, as do certain of the Protozoa. They are conveyed in the blood and lymph, as the parasitic Protozoa are. They are deposited in distant tissues and organs, like the parasitic Protozoa, and they show just the same predilection for certain tissues and organs as do the Protozoa. They are like many of the parasitic Protozoa in the fact that they live almost entirely by osmosis. Like the Protozoa, they sometimes live for long periods of time in the body of the host without any sign of their presence, and perhaps in a state of lethargy, until their vigour and activity are

restored to them by some lowering of the resistance of the host, or by some change in the part in which they have been lying, which renders it more suitable to their necessities. They do not appear to furnish toxines which are dangerous to the health of the host, so that their effects are produced (like the effects of such parasites as *Myxobolus Pfeifferi*) by mechanical causes—destruction of the tissues in which they live and multiply, the stoppage of blood and lymphatic vessels, and the changes consequent on this stoppage. These conditions are naturally more dangerous when they affect the vital parts. On the other hand, when, like the Protozoa, the cancer cells are attacked by pathogenic organisms, bacteria and bacilli (as is almost invariably the case when they become exposed), they are rapidly destroyed, sometimes in great masses, and the effect upon the host is disastrous.

Some cancer cells can live for a long, long time outside the body of the host, although they do not, so far as we know, belong to the class of organisms which are sometimes parasitic, sometimes not parasitic. I am not aware of any investigations to discover the longest period during which cancer cells can exist outside the body of the host. We want

further information on this point. But it is certain that they can live for weeks in glass tubes, and then be implanted as if they were but just taken from the mass in which they lived. At present, the cancer cells can only be implanted with success in animals of the same species as the animal from which they were taken. In this respect, again, they resemble certain of the Protozoa. It may be that, with greater practice and experience, they will be induced to grow and multiply in animals of a different species, but I very much doubt it, just as I doubt whether *Babesia bigemina*—a parasite of cattle—will be successfully implanted in a sheep.

Cancer cells, like the parasitic Protozoa, are never transformed into tissues of the host, and the structures which they cause to be built up are for their own service, not for the service of the host. They are not themselves transformed into any other kind of tissue, nor do they transform the cells of the body into cancer cells. From the moment they are first unmistakably cancer cells, they remain cancer cells, and from that moment they pursue only those two objects which are pursued by the Protozoa—to live and to reproduce. And if they fail in these objects,

both the individual and the species perish. Of this, ample evidence has been furnished in these last years, particularly by the Imperial Cancer Research for animals, and by Sir Alfred Pearce Gould for man.* In reproduction, they breed as true as any Protozoon. Not only do carcinoma cells reproduce carcinoma cells, and not sarcoma cells, but it is invariably the same variety of cell which is reproduced, with the same properties and powers and characteristics.

It has been said that the cancer cells differ from the Protozoa in the circumstance that they are not constant in their method of reproduction—that they multiply by budding or by mitosis, as pleases them, and that the Protozoa never do so.

If all the Protozoa were thrown into a common receptacle for study, they would also be found to vary in their method of reproduction. I believe it is only because the cancer cells have been treated in this fashion that they seem to be subject to no method. But, separate them, and study them in families, and I think it will be found that they are just as bound in this respect as the families of Protozoa. I suspect that the old rule which was

* Gould, Bradshaw Lecture, 1910.

laid down—I do not remember by whom or exactly when—is as correct now as it was: that the cells of carcinoma multiply by endogenous multiplication, and that the cells of sarcoma multiply by fission or by budding. The terms used may be different, but I suspect the facts will be the same.

I will not describe the physiological characters of the cancer cell in my own terms, for fear it should be thought that I exaggerate. I will quote Professor Calkins:

"Functionally the carcinoma cell is a more perfect type than its orderly colleagues of the epithelium. It takes in and assimilates abundance of food, grows rapidly (especially when near the immediate source of food—that is, at the growing edge), and reproduces its kind through the same complicated processes that characterise free living cells. In short, it is a complete animal organism in itself, simulating in many ways the parasitic protozoon, but differing in some of the most important respects connected with the continued life of the latter." *

I understand that the important respects in which the cancer cell differs from the parasitic Protozoa are:

* *Journal of Experimental Medicine*, X. p. 286, 1908.

(1) "That the cancer cell, so far as we know, undergoes no processes analogous to fertilisation." *

(2) "That it cannot live apart from the organism in which it grows; it cannot be cultivated on artificial media, as we cultivate amœbæ and flagellates." †

To the second of these objections it is already claimed by two workers in the Rockefeller Institute that they have cultivated cancer cells in artificial media.

To the first, one can only say that if, in the future, no process analogous to fertilisation is discovered in the life-history of the cancer cells, it is evident that the import of the process of fertilisation will have to be reconsidered.

If the cancer cell does not conform, in all respects, to the laws which are believed to govern the Protozoa, it will still remain "a complete animal organism in itself." A new phylum will have to be founded for it, and laws drawn up appropriate to its life.

* Calkins, *l.c.*

† Calkins, unpublished letter.

LECTURE II

It will now be convenient to consider how far this theory will account for the phenomena of malignant disease, as we know them in man and animals. Dr. Charles Powell White, in his *Lectures on the Pathology of Cancer*,* says: "We can say, then, that cancer is not due to a specific parasite or parasites, but, on the other hand, we can say that cancer cells themselves act as parasites. This view will explain all the phenomena of Cancer." And Dr. James Ewing, in his *Cancer Problems*,† says: "The whole basis, objective and theoretical, of the cancer parasite has been traversed again and again, with the uniform conclusion of those who finish the journey, that the cancer parasite is the cancer cell."

Dr. White's statement is general and sweeping, but I believe it to be in the main correct,

* Manchester, 1908, p. 72.

† Reports of the Collis P. Huntingdon Fund for Cancer Research of the General Memorial Hospital, vol. ii., 1908, p. 24.

although I am not aware of any detailed analysis on which it rests. So far as time will permit, I propose to supply the deficiency.

There are two great phenomena of malignant disease (cancer), which overshadow all the others, and to which most of the other phenomena are subordinate, and on which they are more or less dependent :

(1) The Tumour.

(2) The Metastases.

The tumour may exist without metastases, and there are reasons for believing that metastases may exist without the presence of a tumour.

(1) The tumour is the primary disease, so far as we know it. Until a very few years ago, the presence of a mass was regarded as an essential to the diagnosis of malignant disease. Now we know that the primary—the initial lesion—of cancer (I use the word as synonymous with malignant disease) may exhibit nothing more than a really trivial thickening of a small area of the skin or mucous membrane. From this trivial beginning arise all the various phenomena which go to make up the history of a case of cancer, and from it originate all the misfortunes and sufferings of the individual—

the host. For, if this tiny area be examined with the microscope, it will be found to be composed of cancer cells, which are either massed together, as if without law or order; or which may, on the other hand, be arranged with singular and wondrous skill, so that the appearance of the disease may closely simulate that of a natural tissue or organ of the body. There is also provision for the maintenance of the cells, in the form of vessels, and often of scaffolding or framework, in which the cells are arranged. And there are usually numbers of other cells—leucocytes, lymphocytes, granulation cells for the most part, in the outskirts of the tumour. So that the mass is made up of several elements, of which the essential element is the cancer cell.

All the conditions connected with the tumour depend, directly or indirectly, on the behaviour of the cancer cells. The cells may fail to maintain themselves, in which case the tumour comes to an untimely end. They degenerate, shrink, waste, die, and are devoured by phagocytes. How often this happens, no one can conjecture, but probably much more frequently than is supposed.*

* Dr. Clowes spoke to me of this on the journey up from the meeting of the British Medical Association at Exeter

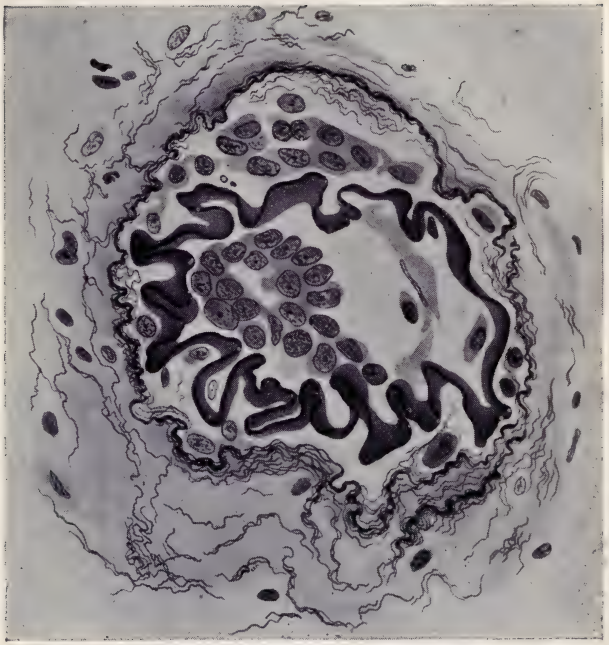

FIG. 10.—Cancerous infiltration of vessel wall (E. E. Goldmann). *Studien zur Biologie der bösartigen Neubildungen*, Taf. IV., Tübingen, 1911.

On the other hand, the cells may thrive, may grow and multiply, in which case the tumour extends its area. When it occurs in the substance of an organ, such as the breast, it may become quite a large lump ; or if it occur in a limb around the bone, it may attain an enormous size. Examine the structure of such a mass, and you will find that the cancer cells and framework have taken the place of the tissues which ought to be there. Fat, fibrous tissue, muscle, have disappeared, or are broken up and separated by groups and masses of cancer cells with their framework. Examine the tissues beyond the apparent limit of the tumour, and you will often find isolated cells or groups of cells between the muscular fibres or in the minute or larger lymphatics.* And you may find little masses of cancer cells projecting into the lumen of a blood-vessel, the wall of which may be destroyed or still unbroken † (Fig. 10).

These conditions are not discovered in all cases of malignant disease, even in all cases of the same variety of cancer of the same part of the body. In some cases, not a single isolated

in 1908, and suggested to me that recovery from an attack of cancer is probably not so very infrequent.

* Handley. † Goldmann.

cell or group of cancer cells will be discovered in the tissues beyond the apparent limit of the tumour. I do not say they are not there, but they are not recognised, so that they cannot be either large or characteristic. Where they are found, however, they may directly produce new phenomena ; for a single cell or group of cells may grow to form a mass in the midst of the muscle or tissue where it lies.

The advance of the tumour is characterised by one great phenomenon—destruction. Every tissue which it attacks is destroyed, and replaced by the cancer cells and their suite. Hard tissues, soft tissues, vascular tissues, and tissues without vessels, are all destroyed—not all at the same pace or all precisely in the same manner. For, such tissues as cartilage and elastic tissue resist the attack much longer than soft tissues, and even than bone. There is also indirect destruction of tissues whose nutrition is interfered with by the growth of the tumour. If the tumour makes its way towards the surface, the epidermis is raised and stripped off, and the mass of cancer cells is exposed. With the exposure of the cells, a new series of events may be expected. Micro-organisms, bacteria and bacilli, gain access to the cancer cells. Sepsis, suppuration, ulcera-

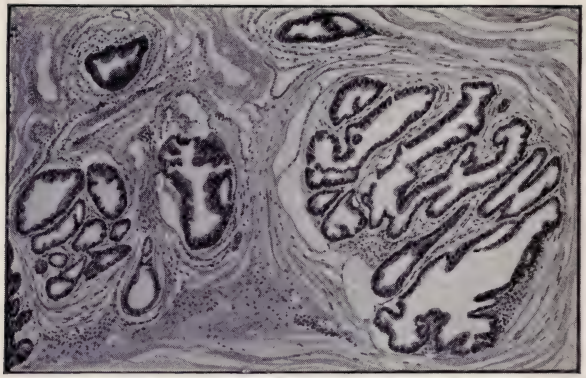

FIG. 11.—Duct cancer of breast.

FIG. 12.—Glands removed from same case (duct cancer) at same time.

tion, and sloughing take place ; and the condition of the host is seriously prejudiced by these occurrences, which may even compass his death. Sometimes, however, the tumour may shrink ; and, even when it is adherent to the skin, may not break through. It undergoes atrophy from the wasting and death of the cells in its central parts. But it is not cured. For, while the centre dies or withers, the margin often flourishes and widens.

In all these circumstances which attend the growth and development of the tumour, there is nothing which does not equally occur in the attacks of certain parasitic Protozoa on their hosts—for instance, *Myxobolus Cyprini* invades, destroys, and takes the place of the kidney epithelium of the carp ; *Myxobolus Pfeifferi* destroys and takes the place of the muscles of the barbel. It is the same story, common both to the cancer cells and to the Protozoa which are not toxic—destruction of the natural tissues, and their replacement by the cancer cells or parasite. And just as the masses formed by cancer cells are attacked by bacteria, and break down and ulcerate when they are exposed, so do the masses formed by *Myxobolus Pfeifferi* break down from similar causes when they reach the surface of the

body and are exposed (Fig. 2). All these phenomena of the tumour are perfectly intelligible if the cancer cell is accepted as an independent organism, pursuing the two great objects which are pursued by the parasitic Protozoa—maintenance of itself and continuation of its species.

(2) And now for the second great phenomenon—Metastasis: the occurrence of masses in various parts of the body, resembling in their elements, and nearly always in their arrangement, the tumour.*

Collections of cancer cells are found, sometimes in one part of the body, sometimes in another, composed, not of cancer cells of different varieties, but of cells of the same variety as those which compose the tumour. Wherever they occur, they are associated with the same conditions as are observed in the tumour—the formation of vessels and a framework, and a satellite collection of other

* Almost all the knowledge we possess of Metastasis—in any case, the useful knowledge—is the result of clinical pathology, not of experimental observation or of laboratory investigation. This is, in itself, so good an excuse for the continued pursuit of clinical pathology, and so admirable an illustration of its use, that it alone would suffice to encourage clinical pathologists, and to furnish proof that the day of clinical pathology is far from its close.

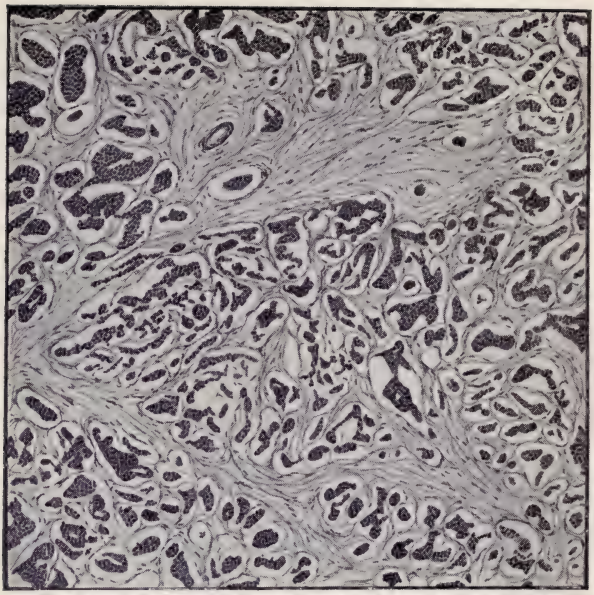

FIG. 13.—Spheroidal carcinoma of breast, removed December 1896.

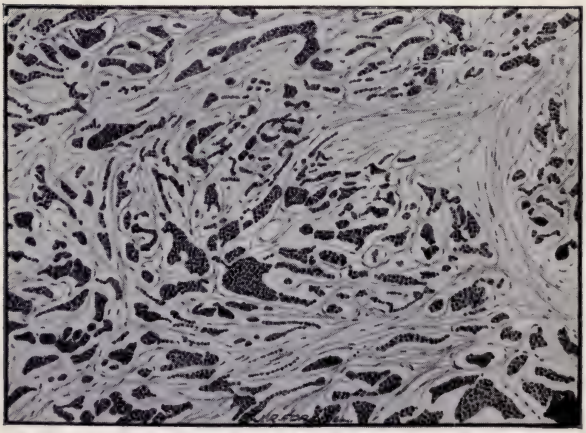

FIG. 14.—Recurrent nodule removed from muscle of same case (13). Removed October 1900 ; patient well in 1906.

cells (leucocytes, lymphocytes, and the like). The grouping of the cancer cells is the same (Figs. 11 and 12; 13 and 14): the substances which they secrete, the degenerations which they undergo, the mode of reproduction —all are those of the cells of the tumour. Every metastasis is, as the Director of our Cancer Research has truly said, a reproduction of the tumour (Figs. 18 and 19), and corresponds with the results of implantation. It is due to the presence of cells from the tumour in those parts of the body in which the metastases occur. On this matter there is practically no difference of opinion, nor is there any serious difference of opinion on the coarse mechanism of metastasis. The cells may be deposited on a surface which is constantly or frequently in contact with the tumour, may become fixed there, and may grow and multiply (auto-inoculation). They may be conveyed in the air or in the food, from the larynx to the lung, or from the stomach to the intestine, and may form metastases in either place. But these are exceptions to the general rule, and are of rare occurrence. The metastases which we see daily are due to the penetration of the cancer cells into the interstices of the tissues or into the lymphatic vessels, along

which they spread, and to conveyance by the lymph and blood (Figs. 10 and 15). They can often be easily demonstrated in the tissues between the fibres of voluntary muscle, for example, and in the lymphatics. But it is wellnigh impossible to detect them in the moving blood and lymph, probably because it is the young and least characteristic cells which are conveyed, and there is so little to distinguish them by, especially when they are on the move. In spite of the absence of direct evidence, the circumstantial evidence in favour of conveyance in the blood and lymph is so strong that it is not questioned, and I need not occupy your time by repeating it.*

* There is really only one point on which there is grave doubt—whether the cancer cells are mere passive bodies in their migration, or whether they are active agents.

Bland-Sutton, in the third of his Lectures on Cancer in the *Clinical Journal* (vol. xxxiii.. p. 186, 1908), says: "I want you to understand, too, how these cancerous cells involve the lymphatics. It is not merely that the cancer cells find their way into the lumen of the lymphatics and then float along like a cork on a stream, or like a fish in a pond; that is not the way they go. One of the most striking features of a cancer cell is its power of invading and eroding any tissues with which it comes in contact. So great is this power of the cancer cell to erode living tissue that it will eat up and form large holes in bones, as these specimens before you testify."

I am disposed to agree with Mr. Bland-Sutton, but I do not know that we are yet justified in using the very decided terms which he has employed.

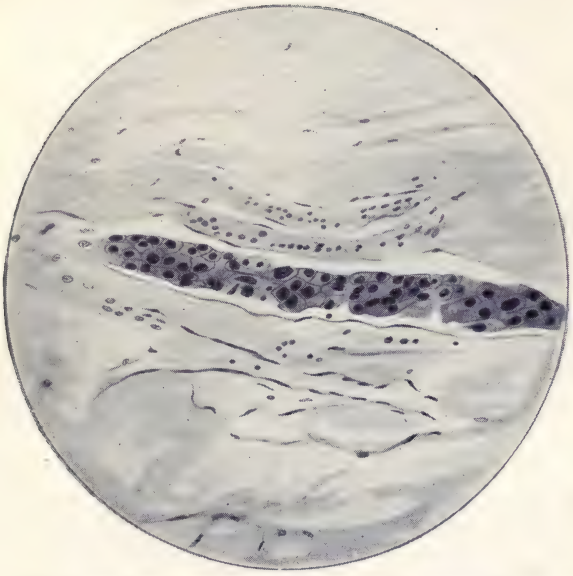

FIG. 15.—Lymph-vessel filled with cancer cells (lymphatic permeation; from Sampson Handley). *Cancer of the Breast*, Pl. III., London, 1906.

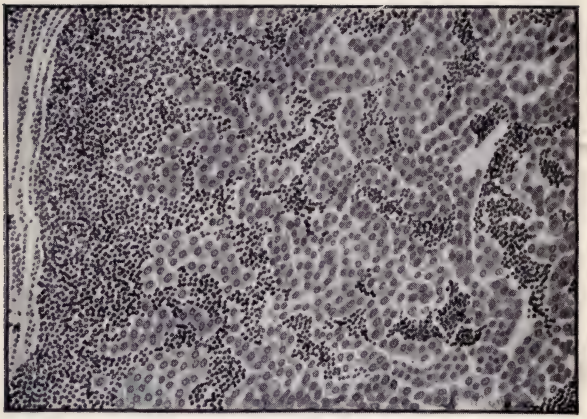

FIG. 16.—Axillary glands removed twenty years after successful removal of the breast.*

* The history of this case is very interesting. In 1895 Sir James Paget sent me a lady whose left breast he had amputated for carcinoma about 1875. The glands had not been removed. About 1885 Mr. Stephen Paget destroyed with the cautery "some carcinomatous tubercles in the right breast." When I saw her in 1895 there was no recurrence in either breast, but a mass of glands in the left axilla, which were easily removed. She came to see me in 1898. There was no recurrence either in the breast or in the axilla on the left side, but there was recurrence on the right breast, for which I amputated the breast (xi. 201).

Seeing the variety of the mechanism of metastasis, it is only reasonable to expect that there should be some variation in the number and seat of the metastases. And so, indeed, there is. Sometimes the metastasis is limited to a single tiny nodule in a distant organ, sometimes to a few tiny nodules within a limited area ; sometimes it is greater in bulk than the tumour, and sometimes it seems as if it had been scattered broadcast, without order or method. Nor is there greater uniformity with regard to time than in regard to seat and size. Metastasis may be present at the moment the tumour is discovered—or it may be deferred for years (Fig. 16)—or it may never occur in cases in which it ought to. No wonder such variations have been a puzzle to those who study cancer, particularly to the experimental investigators. It seems so inconsequent, so void of method, that it has led one of the most able investigators of the present day to aver that the study of cancer in man and animals is rendered peculiarly difficult by the extraordinary variety in the histology and clinical behaviour of the malignant new growths which attack them.*

* Bashford, *Science Progress*, 1907, No. 5, July.

I do not agree with this statement. It rests on a misapprehension, on a false conception of cancer, on imperfect observation, and on the manner in which the life-history of cancer has been studied. If all varieties of cancer in all kinds of animals are studied, higgledy-piggledy — squamous carcinomas, spindle sarcomas, spheroidal carcinomas, myeloid sarcomas—in man and mice and dogs and rats, it is perfectly correct. It would be equally true of the parasitic Protozoa, if they were studied in similar fashion. If Sarcosporidiidæ, Myxosporidiidæ, Coccidiidæ, were all jumbled together, and an attempt were made to describe the histology and clinical behaviour of the jumbled mass, the result would be confusion and profound perplexity. But no naturalist thinks of studying them in such a fashion. Each family is studied separately—not only each family, but each variety—and the characters and life-history of each is gradually deduced with clearness. Precisely the same method must be directed to the study of the organisms of cancer. Each must be studied separately. For more than thirty years I have insisted on the necessity of the separate study of each variety of cancer in the part

in which it occurs.* And Mr. Stephen Paget, more than twenty years ago, in an excellent paper in the *Lancet*,† showed the necessity for this same separate study, particularly in relation to metastasis. To some extent this has been done by the clinical pathologists, and here are some of the results.

Take, first, a round-celled sarcoma. Let it be of the femur and sub-periosteal. It grows very rapidly, and is one of the most surely fatal of diseases. Amputate the limb above it—far above it—and take the bone out of the socket. It is, nevertheless, likely to return in the muscles of the stump. And even if it does not do so, the patient will almost inevitably die of metastasis, even if the tumour was removed as soon as it was discovered. Of all places, the lungs are most likely to be the seat of the metastases. The femoral and inguinal glands are not usually affected. But metastases may occur in distant lymphatic glands, in the skin and subcutaneous tissue, in the liver—indeed, almost everywhere. Most of the patients are dead within a year or

* "Sarcoma and Carcinoma"; "Malignant Disease of the Larynx."

† March 23, 1889: "The Distribution of the Secondary Growths in Cancer of the Breast."

fifteen months. And the instances in which a patient can be claimed to have been cured of this most terrible variety of cancer are so few that they can be counted in units.*

Now take a spindle-celled sarcoma of the testis—also a very deadly disease, but not to be compared in this respect to sub-periosteal sarcoma of the femur. It forms a tumour, often large, in the cavity of the scrotum. It is easy to remove it, and there are many instances in which there is no recurrence in the stump, and the patient is cured by the operation. But there are many more cases in which, at the end of an indefinite period—perhaps a year, two years, or more—a mass is discovered in the abdomen, which grows until it kills the patient. It is formed by metastasis in the glands, in the liver, and other viscera of the abdomen.

Take a spheroidal-celled carcinoma of the breast. The metastases will occur first, and chiefly, in the glands of the axilla ; then in the

* Dr. Coley claims to have cured some cases of sub-periosteal sarcoma of the femur by his injections. We have not been very successful in this country, and I only hear of a very occasional success from the use of Coley's fluid. But it is probable Dr. Coley and his pupils are more skilled in the management of the fluid than the English and Continental surgeons.

liver and lungs, but particularly in the liver.* They may attack the bones—the sternum, the humerus, the femur, and the vertebræ—particularly the vertebræ of the lumbar region. And if the disease recurs *in situ*, it frequently forms numerous little flat nodules or plaques in the skin and subcutaneous tissue.† If the breast and glands are removed, there may be no distant metastases. But the pathologist would be a bold or ignorant man who would assure the patient that the disease would certainly be cured by the operation.

Again, take a columnar-celled carcinoma of the rectum. The metastases will be in the abdominal lymphatic glands and in the liver, in preference to any other part.

Take squamous carcinoma of the tongue, where the limitation of metastasis becomes much more restricted. It takes place in the neighbouring lymphatic glands, and sometimes in the glands on the opposite side of the neck. If the primary disease and the glands are successfully removed, so that there is no recurrence in tongue or glands, there is so little likelihood of distant metastases that they

* Stephen Paget.

† The mechanism of these metastases has been very well described by Mr. Sampson Handley in his book on "Cancer of the Breast."

are practically left out of the account. The possibility is admitted, but the event is so far infrequent that we do not fear it.

Finally, take rodent ulcer of the face. The extension of the disease beyond its apparent limit—the destruction effected by the cells, their tenacity of life and power of multiplication—have long assured for rodent ulcer a place among the malignant tumours. But the cells of which it is composed seem to be quite incapable of flourishing in any other part than the immediate neighbourhood of the tumour, and there are no metastases. I do not say that metastasis never takes place, but it is so rare that its occurrence is not provided for in the pathology of the disease.

Just as the explanation of metastasis is migration of the cancer cells, so the explanation of the seat of metastatic tumours is precisely that which explains the occurrence and seat of the metastases of the parasitic Protozoa—the penetration of the cells into those places which are suitable to their existence—those places in which they can live and thrive and multiply.

Any one case of a particular variety of cancer of a particular part of the body does not run precisely the same course as every other case of

the same variety of cancer of the same part. Nor does any one case of a parasitic protozoon in a particular animal run precisely the same course as every other case of the same protozoon in the same animal. But compare a hundred cases of squamous carcinoma of the tongue with another hundred cases of the same disease of the same part, and let the conditions be similar for each hundred cases as regards operation, etc., and I venture to say that the resemblance of the second hundred to the first hundred cases would be marvellous. I am sure that no greater differences would be discovered than would be discovered if a hundred cases of *Sarcocystis miescheriana* were compared with another hundred cases of the same parasite in the same animal, and not so much difference as would be found if a hundred cases of *Myxobolus Pfeifferi* were compared with another hundred cases, but the barbel were taken from two quite different streams. In the same way, compare a hundred cases of carcinoma of the breast with another hundred cases of the same variety of carcinoma of the same part, and see how little difference there will be between them.

When studied in this fashion, the results are so constant that we, the surgeons, presume

upon them. We trade on them! We do not remove the lymphatic glands in cases of rodent ulcer, because we are confident, however long the disease has existed, that the glands will not become diseased. And we are equally confident that there will not be metastasis in any other part of the body.

We remove the primary tumour and the associated glands for squamous carcinoma of the tongue, with the full assurance that if the operation is successful in preventing occurrence or recurrence in those structures, we shall save the lives of many of our patients.

We amputate the breast, remove the muscle and the contents of the axilla, and dissect away wide areas of the fascia for spheroidal carcinoma. When the disease is not extensive, or rapid in its course, we expect to save the lives of more than half our patients. But we have not the same hope of the result of a successful operation as we have if the operation is successful in rodent ulcer or in squamous cancer of the lip. For the spheroidal cell may thrive and multiply in the liver, the lungs, and bones. And this may happen five or six or more years after the successful removal of the breast and associated structures.*

* In speaking of "successful operations" in the pre-

So with regard to other varieties of cancer in various parts of the body. In all cases our treatment is adapted to what we know, or believe we know, of the course of that particular variety of cancer in that particular part of the body. And if it be charged against us that we are often woefully at fault in our estimate of the effect of an operation, or in our prognosis of an individual case, it must be remembered that the observations on which our present methods of treatment and prognosis are founded have all, practically, been collected during the last forty years, or little more.

Time will not permit me to deal with all the phenomena of cancer as they have risen before my mind in the course of the last few months, during which these Lectures have been in preparation. I shall have to reserve some of them for the publication of the Lectures,* and I

ceding paragraphs, I hope it will be understood that I am only referring to the success of the operation in preventing the recurrence in parts which were diseased.

* During the preparation of these Lectures for publication, I have thought it better to retain the first and second Lectures in their original form, and to speak of some other phenomena of cancer in a short Appendix, which will be found at the end of this Lecture.

shall also have to reserve the consideration of this theory as a working theory of cancer. But there are two or three phenomena to which I should like to refer. The first has puzzled many pathologists for many years. I tried to explain it twenty years ago, with indifferent success.*

It is the occurrence of metastases without the evidence of primary disease. The best examples of it have been observed in the occurrence of squamous carcinoma of the groin glands in sweeps, in whom no primary growth or sore has been discovered by competent observers (Fig. 17). I suggested that the primary disease had "aborted"—in other words, got well—but not before some of the cells containing the material of cancer had been conveyed to the lymphatic glands. My explanation was very near the truth. That cancer should "abort" (get well), was not much in the minds of pathologists twenty years ago. To-day, everybody knows that it does get well, both in animals and human beings,† and many of us are prepared to believe that it

* "Cancer of the Scrotum in Chimney-sweeps and others" (*British Medical Journal*, 1892, i. and ii.).

† Pearce Gould. Bradshaw Lecture, 1910 (Scientific Reports of the Imperial Cancer Research).

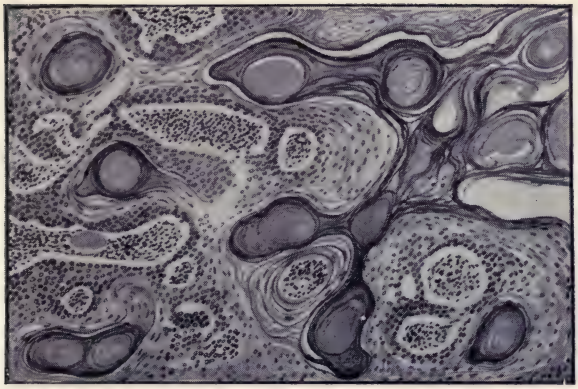

FIG. 17.—Squamous-celled carcinoma of the groin glands of a chimney-sweep, in whom no primary disease was discovered.*

* This case was published in the *British Medical Journal*, 1892, ii. p. 578, by Dr. John Stacy, of Norwich. After the death of the patient Dr. Stacy sent me slides cut from the glands. I do not know whether any similar case has been drawn.

gets well much more commonly than we know of at present. But in these cases, before it does so, some of the cancer cells have already migrated to the groin glands, and have made good their footing there.

The occurrence of ossification, calcification, and chondrification in many of the sarcomata, when the tumour is connected with a bone, or when the metastasis is of a tumour growing from a bone is a phenomenon which has never puzzled me. It seems natural—only what might be expected—that the framework of such tumours should contain bone or cartilage. But I confess it has puzzled me when the tumour is of a part which has no connection with bone or periosteum. For instance, such a tumour is sometimes (though very rarely) found in the female breast. Why should cells derived from the glandular or connective tissue of the breast command a framework or scaffolding in which bone or cartilage are prominent constituents? Bashford explains it on the grounds that such conditions occur in association with inflammatory processes. He shows how frequently it occurs in mammary tumours in the dog, and says, "This seems to demonstrate that the connective tissue of the dog is very liable to such metaplastic changes,

just as the connective tissue of the rat or of the mouse is liable to the changes characteristic for these animals." *

There is one phenomenon of cancer which no theory explains—the constancy with which spontaneous cancer begins at one point instead of many. It can scarcely be made to fit in with the theory of "removal of restraint," but it does not threaten the stability of this, or many other theories. At present I have no explanation to offer of it.

Reviewing, in a few sentences, the application of this theory to the phenomena of cancer, I will not undertake to affirm that all the known phenomena of cancer can at once be explained by it, but it *does* offer a ready explanation of the first great phenomenon of cancer—the tumour—and of all the changes which may occur in it. It offers an explanation of Metastasis—the other great phenomenon of cancer—of the reasons why it occurs, why it occurs in one place rather than another, of deferred metastasis, of metastasis without primary tumour. In fact, it explains so simply so many of the phenomena of cancer

* Fourth Scientific Report of the Imperial Cancer Research Fund, p. 173.

that it is necessary to make diligent search to discover the two or three phenomena which are not explained by it. And of these it may be said that there is not one of them which endangers the acceptance of the theory, and that they are equally inexplicable by any other theory which has yet been advanced.

It fulfils also the conditions laid down by a writer in the *British Medical Journal*,* who pointed out that, to make my case good, my parasite must be tried by the laws laid down by Koch—to wit: "A specific micro-organism must be constantly associated with a given disease; it must be isolable and studiable apart from the disease, and when introduced into a healthy animal it must be able to reproduce the disease in that animal; and in the animal in which the disease has thus been experimentally reproduced, the organism must be found under the original conditions."

It fulfils these conditions with a fidelity which is remarkable. The only one of them on which any dispute could arise would be whether the cell is "isolable and studiable apart from the disease" in the sense in which Professor Koch used the expression. If that

* Dr. Fred Wright, *British Medical Journal*, 1911, I. 51.

is all that is lacking, we are not likely to have to wait long for it. Indeed, Carrel and Burrows maintain that they have already solved that problem in the Rockefeller Institute of Medical Research.*

I now come to the last part of my task: Where does the cancer cell come from?

Six years ago,† I summed up the evidence in favour of the only two views which could reasonably be put forward—*Entrance from without*, or *formation within* the body—and came reluctantly to the conclusion that the evidence of "*formation within*" was stronger than the evidence in favour of "*entrance from without.*" I say "reluctantly," because it led to the logical conclusion that new species of living creatures are created from a source and in a manner which has never hitherto been imagined. Nevertheless, during the last six years the evidence in favour of "*formation within*" the body has grown steadily stronger, while nothing has been added to the evidence

* Alexis Carrel and Montrose Burrows (*Journal of the American Medical Association*, 1910, vol. 55, pp. 1379, 1554, 1732). Mr. Arbuthnot Lane told me he had seen the specimens of growing sarcoma cells in the Rockefeller Institute.

† Bradshaw Lecture.

in favour of "*entrance from without.*" I cannot stop to dwell on the points of each piece of evidence, but must content myself with enumerating them :

(1) The resemblance of the cancer cells to those of the natural tissues in which the cancer appears to start.

(2) The resemblance of the secretion of the cancer cells to the secretion of the natural cells.

(3) The resemblance of the degenerations of the cells to those of the normal cells (fatty, caseous, calcareous, etc.).

(4) The resemblance of the grouping of the cells to the grouping of the natural cells.

(5) The resemblance of the phenomena of reproduction in the cancer cells to those of the natural cells which they resemble.

All these may be regarded as traits of atavism, and it is upon these that the explanation of some of the phenomena of cancer rests. Students of cancer, Research workers, biologists who have studied cancer, are all, practically, agreed that the cancer cell is derived from the cells of the part in which it takes its origin, or appears to take its origin, and they are bent on finding an explanation of the reasons which lead the cancer cell to behave so differently

from the cells from which it is derived. Escape from natural restraints, the acquirement of the habit of growth, the theory of embryonic rests, chemical stimulation, a self-contained and ordinary invisible micro-organism living in symbiosis with the cell—these are some of the theories by which learned men have sought to explain the strange conduct of the cancer cell. Empty phrases! They might account for variations in colour, size, shape, secretion, degeneration, physical activity—for a multitude of the variations from the normal cell exhibited by the cancer cell—but how can any of them account for the vital difference which I will express in two short sentences? Implant the normal cell, and you cannot make it live. Implant the cancer cell, and you cannot kill it.

There is one, and only one explanation of the conduct of the cancer cell—that it has been endowed with that wondrous gift which no man has seen, and which no man can understand—the gift of life; and that, owing to that gift, it has become an independent creature, a new creation of living thing. The host, in which it dwells, has fashioned it out of his own tissues and in the likeness of his tissues, and—to borrow the figurative lan-

guage of Scripture—the Creator has breathed into it the breath of life, and it becomes a veritable Frankenstein's monster, bent on the destruction of its host. After ages of past and present civilisation, during which searchers and philosophers have sought to explain the origin and nature of life, we have come no farther than this, and he who discovers the true origin of cancer will have solved the enigma which has hitherto baffled the searchers and philosophers in all ages and of all countries.*

If the cancer cell be in truth a new creature, to what class of creature does it belong? It is nearest to the Protozoa—so near, indeed, that it is difficult to keep it out of the Protozoa. Every new observation of the last six years, every new discovery, has brought it nearer to the Protozoa. But the biologists will have none of it. I must therefore make a special place for it, and provide it with a name. It shall be *Unicellula cancri*. And, for the different varieties, the shape of the cell can be expressed in simple terms which will be familiar to us all. On the one hand, *Uni-*

* "No power of genius has ever yet had the smallest success in explaining existence." Emerson: *Representative Men* (Macmillan, London, 1893, p. 314).

cellula (*cancri*) *squamosa, Unicellula spheroidatis*, etc.; on the other hand, *Unicellula* (*cancri*) *fusiformis, Unicellula rotunda*; and so on. These names will serve still, even if the cells eventually join the great phylum of the Protozoa.

I am perfectly conscious of the far-reaching consequences of admitting that unicellular bodies, derived from such a source, are a new species of created beings, but there is no alternative. The facts are plain, and cannot, I believe, be otherwise interpreted. If the theory is false, I can only say it is very remarkable that it should explain, in so satisfactory a manner, the chief, and nearly all the subordinate phenomena of cancer.*

In conclusion, I should like to tell you a parable. A learned professor, walking in the desert, observed a curious little object on the ground. It had a rounded snout and flattened

* Mr. Darwin, in the last chapter of the *Origin of Species*, says:

"It can hardly be supposed that a false theory would explain, in so satisfactory a manner as does the theory of natural selection, the several large classes of facts above specified. It has recently been objected that this is an unsafe method of arguing; but it is a method used in judging of the common events of life, and has often been used by the greatest philosophers" (*Origin of Species*, 6th Ed., London, 1889, p. 421).

head, large eyes, a flattened body, short fore-legs, and very long hind-legs. It sometimes walked and sometimes jumped. The professor asked whence it came, and it replied, "I am a child of the desert, born of the grains of sand." This astonished the learned man. He took it home with him, and called together many of his friends, and set the little beast in their midst.

They all looked at it, and said it must be a frog, for it looked like a frog, and behaved like a frog, particularly in its ability to jump. But when they heard its origin they were all amazed, and each one gave his explanation of the occurrence. One said, "It is a changeling —it is not what it looks to be"; another said, "It is surely made to swim, for its feet are webbed, and having no water to swim in, it has acquired the habit of jumping"; a third said, "It has been gingered"; a fourth said, "Some restraint must have been taken off it, to enable it to jump." And the professor himself said, "No, it has a flea inside which lives within it as its familiar spirit, and that gives it the power of jumping."

Then the professor said to the little object: "We are very sorry for you. You are neither animal nor vegetable, for neither animal nor

vegetable can be created from the sands of the desert. There is, therefore, no place for you among living creatures."

The little creature jumped and crawled away. But as it did so, it looked back at the group of learned men, and said, "There is no place in the living world for me owing to the misfortune of my birth! Thank you, gentlemen, but I have already found a place for myself, and you will find it very difficult to oust me from it."

APPENDIX TO LECTURE II

On Certain Phenomena of Cancer, omitted in the Lecture for lack of time

1. The cause of the *Age Incidence* of spontaneous cancer is very difficult to understand. It is well known that the liability to almost every variety of spontaneous cancer increases as the age of the animal advances. It was at one time thought that the tissues of young animals were not fitted for the maintenance of cancer. Experimental investigation has taught us that this view has no foundation in fact. Cancers which are implanted grow just as well, if not better, when they are implanted into flourishing young animals, than when they are implanted into old animals.

Although I am not disposed to agree with all the findings of the Statical Committee of the Imperial Cancer Research on the increased proportional liability of every person who grows older to every variety of malignant disease, even after such corrections as I should make, the fact remains that spontaneous cancer is a disease of middle-aged and old people. I do not know of any hypothesis or theory of cancer which accounts

for this phenomenon. I shall make no attempt to explain it. It seems to me that it is consistent with almost any of the current theories of cancer. And it may, therefore, as well be accepted in the hope that an explanation of it may be forthcoming at some future time. The only statements which have appeared to me to be erroneous are those which would make it apply to every variety of malignant disease in every part of the body. Many years ago I found that sarcomatous tumours of the long bones were generally first observed between the ages of fifteen and twenty-five. I also found that malignant tumours of the testicle appeared in boys of one year to ten years of age, then became much less frequent, to become more frequent again after forty years of age. Other surgeons who have studied the same varieties of cancer in the same parts of the body have formed the same opinion. I should therefore say, from my own study of a number of cases, that the liability to every variety of malignant disease increases regularly and proportionately as the age of the individual increases throughout life ; but that there are exceptions to this general rule, especially in the sarcomatous tumours of the long bones and sarcomatous tumours of the testicle, etc.

Again, rodent ulcer has often been regarded as particularly a malignant disease of advanced life. But, when the histories of individual cases of rodent ulcer have been inquired into, it has been found that they run back for twenty or twenty-five years, and therefore fix the date of the com-

mencement of the disease at twenty-five to thirty-five years instead of forty years and upwards.

2. *On Difference in the Course of the same Variety of Cancer of the same Organ, which is sometimes observed.*—One hundred cases of the same variety of malignant disease originating in a particular organ or tissue ought, theoretically, to run the same course as another hundred cases of the same variety taken from the same part. Practically, there can be little doubt that they do so. But there are modifications of this proposition which would seem difficult to explain. Attempt to apply it, for instance, to squamous carcinoma of the larynx, and, unless certain provisions are made, it will fall through. For the course of squamous carcinoma of the larynx will depend, to a large extent, on whether the carcinoma grew from the intrinsic or the extrinsic parts of the larynx. Squamous carcinomas which grow from the intrinsic parts of the larynx are notoriously much less acutely malignant than squamous carcinomas of extrinsic origin. They display their milder malignancy in more ways than one: for instance, they grow slowly; are often slow in recurring after removal; are sometimes cured by a simple intra-laryngeal operation (such as the nipping off the tiny area of disease with a pair of cutting-forceps); and the lymphatic glands of the neck are not involved. A large proportion of the patients from whom the disease is removed by thyrotomy are completely cured by the operation: yet the lymphatic glands are not removed. Com-

pare with such a course as this, the course of squamous carcinoma of extrinsic origin (epiglottis, ary-epiglottic folds, arytenoids, inter-arytenoid folds). The growth of the tumours is much more rapid; they require a much more extensive operation for their removal, and even then are much more prone to recur. The lymphatic glands are early and often widely involved. In a word, extrinsic carcinoma is, speaking in general terms, a formidable and fatal disease; while intrinsic carcinoma is one of the least dangerous of squamous carcinomas. Wherein does the difference consist? Certainly not in the structure of the disease, for the structure of the two carcinomas may be identical. No; it consists, I think, largely in the anatomical characters of the intrinsic and extrinsic structures from which the tumours respectively grow. The intrinsic parts are less soft, some of them less vascular, all of them poorly furnished with lymphatics; and the communication between the lymphatics of the interior of the larynx and the lymphatic glands is, as injections have shown, very sparse. On the other hand, the extrinsic structures are abundantly provided with lymphatic vessels, and the connection between them and the lymphatic glands is very free. De Santi has drawn attention to these important matters in *Malignant Disease of the Larynx*,* and has attributed the comparative immunity of the glands in intrinsic carcinoma to these

* London, 1904, pp. 16 *et seq.*

causes. And this is the more probable because intrinsic cancer does affect the lymphatic glands when it has existed a long time, and particularly when it has grown from the interior into the outer parts of the larynx.

3. *On Metastasis and Cross-affection of Lymphatic Glands.*—Various interesting problems present themselves in connection with metastasis in lymphatic glands. If a particular variety of cancer is prone to form metastatic growths in the neighbouring glands, why are the metastases so frequently limited to those glands? Let me give two concrete examples. Spheroidal-celled carcinoma of the breast affects the axillary glands. Even when the cells have been migrating for months, or even years, and there are metastases in other parts of the body, the metastases are not very prone to affect the more distant lymph glands; yet it might have been expected that lymphatic glandular tissue would prove an attractive medium in one part of the body as well as in another. Again, squamous carcinoma of the tongue very rarely attacks the axillary, inguinal, or abdominal glands: yet its predilection for lymphatic glands is very pronounced; and, after it has begun to migrate, it might be expected that metastases would be found in some one or other of these distant groups of glands. There is the more reason to expect it on account of the occasional deviations from the usual course which are observed in cases of cancer of the tongue. Not only are there cases in which the glands on both sides

of the neck are the seat of metastasis, but every surgeon is acquainted with cases of what has been termed "cross-affection" of lymphatic glands in connection with squamous carcinoma of the tongue, cases in which the primary disease—the tumour—is situated on one side or border far from the middle line, while the glands on the opposite side of the neck are diseased and those on the same side are not at all enlarged.

Speaking generally, the neighbouring lymphatic glands are affected much as we should expect them to be affected: those nearest to the tumour first, the more distant glands in their turn. I suspect that the resistance of the glands is overcome—and not the resistance of the glands alone but of many other tissues and organs—by repeated entrance into them of cancer cells, not by a sudden assault. Many of the cancer cells may be destroyed by the resistance of the host; and the resistance of the tissues, where they have fought for life and lost it, may be gradually lowered by that very circumstance.

LECTURE III

THE WORKING THEORY OF CANCER FOUNDED ON THE TWO PREVIOUS LECTURES

WHEN I was a young man there were a good many surgeons attached to the hospitals in London who spoke of themselves as " practical surgeons." They not only exhibited no interest in pathology and in the scientific problems connected with their trade of surgeon, but they held such things in scorn and laughed at those who did pursue them. To them surgery consisted in the diagnosis of disease and in the treatment of it, particularly by operation. They prided themselves—often quite justly—on their neatness, skill, and boldness. They sometimes heard it stated that pathology is the foundation of surgery. But the statement had no meaning in their ears, and they seldom gave themselves the trouble to discuss it or even to consider it.

Practical surgeons may still exist, but they are not now in evidence as they used to be. They no longer make a boast of their ignorance of pathology and the scientific side of surgery, and now it is rather the fashion to admit that pathology is the foundation of medicine and surgery. It is a good sound principle ; rather an abstract proposition than a practical suggestion. It is only the weak and unpractical men who allow themselves to be influenced in their diagnosis and treatment of a disease or accident by the views of its pathology which happen to prevail at the moment.

As a matter of fact, I am sure that physicians and surgeons, scientific or practical, are always to some extent influenced in their diagnosis and treatment of accident and disease by the idea which they have in their minds of the nature—in other words, the pathology—of the disease. But few persons are conscious of the extent to which they may be, and often are, influenced by the pathology of the day in relation to a particular disease. To illustrate this statement, I shall take the single example of cancer and of the influence of the pathology of the day on the treatment of cancer as I have actually myself known it.

The Humoral and the Local Theories of Cancer

In the course of the last sixty years two great theories of cancer have held the field: the *humoral* theory and the *local* theory. (I am not, of course, speaking of minor theories, of the parasitic origin of cancer, etc., which have sprung up later; but solely of the two great theories of cancer which were discussed by pathologists and scientific surgeons in all countries.) Was cancer in its early stages a local disease, which became constitutional as it advanced? Or was it from the beginning due to an unsound state of the blood?

I do not know how long the humoral theory had received the support of the scientific surgical world, nor do I know who was responsible for it in the first instance. It was maintained by Mr. Paget, in his lectures on Tumour at the Royal College of Surgeons, just over sixty years ago. My copy of his Lectures (1853) is, I believe, the first edition. Two or three extracts from it will suffice to state his views.

For the present I will say only that I think malignant tumours are local manifestations of some specific morbid states of the blood;

. . .* The general history of cancers and their analogy with other diseases that are, in the same senses, specific and constitutional, imply that, before the formation of a cancerous growth, two things at least must co-exist—namely, a certain morbid material in the blood, and some part appropriate to be the seat of a growth incorporating that material, some place in which the morbid material may assume, or enter into, organic structure.†

This was the pathology of cancer which was taught at St. Bartholomew's Hospital when I became a student in the middle 'sixties. Such were the reputation and eloquence of our great master that, if his views had differed from those of all other pathologists, he would have carried with him a large body of disciples. But they were the generally accepted views, and he happened to be one of the greatest exponents of them.

Now, see the pernicious influence of them on the treatment of cancer. I again quote from the Lectures. Mr. Paget did not deal with the general question of operations for cancer, but he discussed the question of operation against cancer of the breast. For the study of the

* *Lectures on Surgical Pathology*, by James Paget, F.R.S., vol. ii., London, 1853, p. 18

† *Loc. cit.*, p. 529

results of operations, he took two series of cases of scirrhus cancer. The first was a series of sixty-six cases in which no operation was performed. Of this series, he says: "The average duration of life, from the patient's first observation of the disease, is a little more than four years." * The second was a series of "forty-seven cases, in which the cancer was once or more removed by operation; the average duration of life, after the first observation of the disease, was again something more than forty-nine months." † And, to leave no doubt regarding his opinion of the value of operation, he says, a few pages farther on:

In deciding for or against the removal of a cancerous breast, in any single case, we may, I think, dismiss all hope that the operation will be a final remedy for the disease. I will not say that such a thing is impossible; but it is so highly improbable, that a hope of its occurring in any single case cannot be reasonably entertained. ‡

Under this pessimistic pathology, the most that was ever expected from an operation was

* About forty-nine months. Paget, *loc. cit.*, p. 344.
† *Loc. cit.*, p. 346. ‡ *Ibid.*, p. 351.

that the patient might die a little less miserably. The disease was often advanced before it was removed ; the operation was quite inadequate ; the objects of the surgeon were to obtain an immediate good result of his operation and to prevent recurrence in situ. But his operation was seldom wide enough to secure the second object. There was no hope, either for the present or the future. To the very end of their surgical lives, many surgeons of the surgical generation before my own—such men as Sir Thomas Smith—were under the influence of these views, and I have heard the expression many times : " Once cancer, always cancer."

I do not remember when or where or how the theory of the *local* origin of cancer came before the pathologists and surgeons, or whether it was a British or a Continental inspiration. It was a very happy inspiration, and humanity has occasion to be very thankful for it. I have no recollection of discussing it and suddenly being struck with the belief that it was true. Probably, conversion came slowly from the more careful study of individual cases of cancer and from the slow discovery that operations were more successful than they had been believed to be. I can well remember occasion-

ally drawing the attention of members of the permanent staff (when I was Surgical Registrar to the Hospital and working at the Pathological Society) to such successful cases. The reply was always: "Well, you may be sure it was not a case of cancer!" And, if the microscopical examination was adduced in proof of cancer, incredulity was expressed, which was by no means flattering to a young pathologist. The principle on which the results of operations for reputed cancer were regarded by the humoral pathologists was simple and ready of application; if removal of a cancer were followed by recurrence and death, there was no doubt of the correctness of the diagnosis; if there was no recurrence, and the patient lived and remained sound, it was because the disease was not cancer, whatever the microscopist might say.

I suppose the steady accumulation of observations, supported by more experienced microscopists, and the more careful recording of cases of cancer were the chief circumstances which shook the humoral theory of cancer. There were, too, certain weak points in the armour of its advocates. Thus, Mr. Paget had been obliged to admit in his Lectures on Epithelial Cancer, "that in some cases per-

manent recovery, and in some a long period of health, follows their removal." *

Gradually belief in the curability of cancer was established. Hope was infused into the minds of surgeons and their patients. Operations for cancer were better planned; they were far better performed than they had been; they were performed at a much earlier period of the disease; and, thanks to the discovery of antiseptic surgery, they were performed with much less distress and danger to the patient; until, in these later years, operations for cancer have been extended far beyond the limits they were formerly intended to observe, and, I am afraid, sometimes beyond the limits which prudence and a better knowledge of pathology would justify.

It must not be imagined that all this was accomplished without a great deal of opposition, or that it was carried through in the course of a few years. Even when it was evident that the humoral theory, even in the strict sense of the humoral pathologists sixty years ago, could no longer be maintained, it was by no

* *Loc. cit.*, p. 474. It is very important that a few pages farther on—p. 478—he collects "from the facts of this Lecture the grounds which seem to justify the inclusion of this disease under the name of 'cancer.'"

means abandoned. The old humoral pathologists and those who would not admit the local origin of cancer, spoke of the constitutional origin of cancer ; and discussions took place and battle was waged, with varying success, by the adherents of the two theories, and would probably still be waging had not the question been definitely settled by experimental investigation by our own and other Cancer Research Associations in the course of the last ten years.

Since then the local origin of cancer holds the field. The object of the surgeon is to remove it early, while it still remains a local disease. He may remove the tumour alone, with a more or less wide area of the tissues outside into which the cancer cells may have escaped ; and he may extend his operation to the associated lymphatic glands, whether they are obviously cancerous or not, provided experience has taught him that they are liable to become cancerous. His working theory is plain and simple : it is to remove the whole of the existing disease—in fact, to get all the cancer cells out of the body of his patient. If he can do this, the patient will be cured.

In spite of errors of judgment, of ignorance of the special pathology of cancer of different

parts of the body, of faulty application of operations, and of all the pitfalls which attend the steps of even the most prudent and accomplished surgeons in the exploration of new fields of operative surgery, the advantages which have been gained for cancerous persons by the institution of a good working theory of cancer for a bad one are greater than the mind of man could have conceived. So far as the surgery of cancer is concerned, I was reared by pessimists, and lived in their society and held their views, and was myself for some time a fatalist on the subject of cancer. For some years past I have been living in the society of optimists, to the formation of which I did contribute, though but a small part. Their enthusiasm seems to know no bounds; and the optimism of some of them is so great, that I verily believe they regard every variety of cancer as curable by operation, provided the operation be sufficient and the disease in an early stage. However, it is a much better atmosphere than the other, good both for the surgeon and the patient, and I do not complain of it.

Working Theory

My theory is neither *Local* nor *Humoral:* it is both, it is first *Local* and secondly *Constitutional.*

1. It is *Local,* in so far that our belief is now well founded that spontaneous cancer is, at its commencement, a local condition. If we turn our backs upon the question of its origin, and regard it just as we find it in the body, it is to all intents in exactly the same relation to the host as most micro-organisms which have entered the body from without, and which are fitted to live in it. Cut it freely out, just as a primary syphilitic sore is sometimes cut off the prepuce, or a little tuberculous sore is cut out of the tongue or tip of a finger, and, if the micro-organism which each of the three primary lesions contains is limited to the lesion, the attack will be cured by the operation. The host may suffer from subsequent attacks of the same nature, but that particular attack is cured. The operation is frequently successful in tubercle, frequently in cancer, less frequently probably in syphilis.

2. *Constitutional.*—But if the micro-organism has already begun to travel (migrate), the disease can no longer be considered to be *Local,*

In each case the micro-organism has broken bounds, and may reach some part of the body in which it can live and multiply. It may reach some place where it may still be cut out with success. This is particularly the case with the glandular affections of tubercle and cancer ; so little the case with syphilis that it is rarely tried.

In most cases of all three diseases the surgeon abandons the attempt to cure by removal, and the only hope lies in the resistance of the patient, assisted by medicine and other remedies. For syphilis the results are, in percentage, exceedingly good ; many patients are cured and the spirochæte dies or is destroyed. For tubercle they are not bad. Fresh air, fit food, cleanliness, tonics, cod-liver oil, and tuberculin cure many patients. The tubercle bacillus dies or is destroyed. For cancer the case is very different. We have no specific medicine for cancer, no general measures (such as we use in tubercle) in which we place the least confidence. The cancer cell is not habitually influenced (or likely to be killed) by drugs, or inoculations, or diet, or air, or by any known treatment. When once, therefore, the cancer cell has broken bounds, the fate of the patient might be regarded as sealed and

all hope lost. Practically, this view prevailed until recently, but it is largely modified by our better knowledge of cancer, particularly that which depends on experimental investigation.

Why Cancer Cells which have Broken Bounds do not always Kill

For cancer cells which have broken bounds do not always kill. Some, such as those of rodent ulcer and recurring fibrous sarcomata, are quite incapable of living and multiplying in other organs and tissues than those in which or in the vicinity of which the disease first appeared. Others may be so feeble that they are not able to live and multiply, even in those tissues and organs which are generally suitable to the needs of this particular variety of cancer cell. Or the resistance of the host may be so strong that the migrating cancer cells are not able to overcome it.

These are not matters of mere conjecture: experimental investigation * has established them beyond dispute. We have learnt that cancer cells of the same variety are not all possessed of equal vigour, and that the resistance

* Imperial Cancer Research.

of different hosts varies within very wide limits. Further, clinical observation has taught us that an attack of cancer may be severe or mild, like the attacks of so many other diseases. I do not mean that one variety of cancer is more fatal than another—spindle-celled sarcoma, for instance, than rodent ulcer—or, that the same variety of cancer is much more fatal in one part of the body than another—squamous carcinoma of the tongue, for example, than squamous carcinoma of the lower lip or scrotum —but that two cases of the same variety of cancer in the same part of the body may vary enormously in their severity. Take, for example, two cases of spheroidal carcinoma of the breast in women of the same age. In the one case the tumour will grow four times as fast as in the other case, the glands will be early affected, and the case will run its course in a year or eighteen months. In the other case the tumour grows so slowly that it is still quite small at the end of four years, the glands are not affected, there is no distant metastasis, and the patient is not aware that she is suffering from a serious disease.

There has been, as long as I can remember, an impression among surgeons that cancer, when it attacks young people, is likely to run

a rapid course—much more rapid than that of the same variety of cancer of the same part of the body in an aged person. I do not attack the impression, for I really do not know whether it is correct. But the obverse must not be relied on—that cancer runs a very slow course in aged people. I have many times seen persons seventy and eighty years of age suffering cruelly from cancer which might have been removed two or three years previously; but the operation had not been performed because the opinion had been expressed that the disease would run a slow course in so old a patient, and would never be likely to cause serious pain or trouble.

These differences have been well known for many years, and have been attributed to various causes. Now we should certainly ascribe them to difference in vigour of the cancer cell in the different cases, and to difference in the resisting power of the tissues of the different hosts. How much is to be ascribed to each of these two great factors we are not in a position to state.

There is reason to believe that in some of the cases the vigour of the cancer cell and the resisting power of the tissues of the host may undergo considerable change. A severe case

may become much less severe, and a mild case may become active, and even severe. In the first set of cases we assume that the vigour of the cancer cells has diminished, and that the "strain" is changed in quality, or that something has occurred to strengthen the resisting power of the tissues of the host. In the other set of cases we assume that a more vigorous "strain" of cells has taken the place of those which formerly grew out of the tumour, or that the resisting power of the tissues of the host has been lowered.

The lowering of the resisting power of the tissues of the host sometimes appears to result from what may be termed an accident. Most surgeons have listened to the story of the patient of how the glandular enlargement he is examining came suddenly after very free use or straining of the arm. The breast had been removed a long time ago, but the glands had been left. I suppose that most of us are disposed to treat this story with small belief, feeling that it is due rather to the wish of the patient that it were true than to conviction that it is true. But I suspect it is far more frequently true than we are disposed to believe, and I will give two cases in point:

Some years ago a gentleman consulted me on a

hard glandular mass in the upper carotid (parotid) region. Three or four days previously, at an evening entertainment, he had sat in a seat where, for two or three hours, a cold draught of air had played upon the side of his neck. The following day his neck was stiff and swollen. And so it remained, for it was due to a cancerous affection of the glands secondary to an epithelioma of the tongue, which had been removed by Sir Jonathan Hutchinson a few months previously.

In December 1895 I removed the left border of the tongue for a small epithelioma which had developed on a patch of leucoplakia. The glands of the neck were not removed, for I had not yet begun to remove them as a routine operation. The patient remained quite well, until the beginning of 1898, when he contracted mumps from his sons. The attack of parotitis on the right side subsided within the usual time, but the attack on the left side did not subside, a hard fixed mass remained in the neck. It was not a proper case for operation, because the tumour was so fixed ; and he died of it in the course of a few months after I last saw him.

Ten years ago these cases would have been explained by suggesting that the " chill " and the mumps had drawn a quantity of blood into the neighbourhood of the lymphatic glands, and that the glands had in consequence been able to furnish better sustenance to the cancer cells. The terms in which we speak of these phenomena are of small importance. There was no recurrence in the tongue in either

case. It must therefore be assumed that the cancer cells had already migrated to the glands before the operation on the tongue, and that they had remained lethargic there until the conditions had been disturbed by what may be spoken of as an accident.

In cases, then, in which the cancer cells have broken bounds and are wandering or migrating, the hope of the patient lies in these factors: (1) in the inability of the cancer cells to exist and flourish at a distance from the tumour; (2) in the possibility that the cancer cells in the individual case may be wanting in vigour; and (3) in the possibility that the resisting power of the host may be high.

The first of these factors requires no treatment; the second is quite beyond our control at present; and the third has been, for some years, constantly before us—so much so that the attempts to discover a specific against cancer has given way, in the minds of most scientific physicians and surgeons, to an attempt to discover some means of increasing the resisting power of the host. This is the object of experimental investigation in laboratories; and means have been discovered of raising the resisting power of the tissue of animals, but

not against the spontaneous occurrence of cancer. These means have not been successfully applied, hitherto, in human beings. Those which have been tried are, for the most part, empirical. But some of them rest on observation and some on theory. Coley's treatment is an example of a method resting on observation ; Beatson's (removal of the ovaries) of a method resting on theory. As to the empirical methods, they are legion. Special diets ; the avoidance or taking of particular articles of food ; drugs ; animal extracts ; external applications ; preparations made from cancerous patients and cancerous tumours—these are representative of the means employed to " kill the cancer," or to raise the resistance of the host.

The Migration of the Cancer Cell

The application, then, of this theory as a working theory of cancer reduces itself to a consideration of the migration of the cancer cell on the one hand and the resistance of the host on the other. As regards the migration of the cancer cell, we have to ask ourselves whether the cells of every variety of cancer migrate whether the cells of every case of the same variety of cancer migrate at the same time and

to the same extent ; and when do cancer cells migrate ?

1. *Do the Cells of Every Variety of Cancer Migrate ?*

I do not know of any data to settle this question. The proof of migration is the presence of metastasis. It may be maintained that the cells of those tumours (like rodent ulcer) which do not produce metastasis, do not migrate. I am disposed to think that they do migrate, but that they cannot find subsistence in the organs and tissues which they reach.

2. *Do the Cells of Every Case of the Same Variety of Cancer Migrate at the Same Time and to the Same Extent ?*

Here, again, we are obliged to depend rather on conjecture than on ascertained facts. But, such evidence as there is, strongly suggests that there is very considerable difference both in respect to time and to extent. Quite apart from the variations observed in the occurrence of metastases in a series of tumours of the same variety in the same part of the body—for instance, a series of tumours of the breast, where the variations might be attributed to differences in the resisting power of the tissues

of the respective hosts—the variation in the rate of growth of the primary lesions (the tumours) and the great difference which microscopists find in sections of a series of primary lesions (tumours) point very strongly to this conclusion.

In some cases the tumour is very well defined both to the naked eye and to the microscope. The cancer cells are not numerous for that variety of tumour as compared with other tumours of the same variety. They are not observed in the tissues outside the apparent limit of the tumour, and the general aspect is a lack of activity. The reports of microscopists on such tumours are that they are "slow-growing." In forming this opinion they also take into account the arrangement of the cells, and are disposed to consider those tumours less malignant in which the cells are arranged in a very orderly manner, so as to represent more or less normal tissues. They may be correct in the opinions which they express, but I often think they far exceed the limit of the scope of the microscopist. Many of them know little or nothing of the clinical pathology of cancer. And they do not understand that the prognosis of an individual case of cancer depends on all the conditions of the case, and should not be

hazarded on one particular condition by persons who are not in possession of all the other conditions.

In other cases, even when the tumour is well defined to the naked eye, the cancer cells are very abundant, grossly formed, irregular in size and shape, and are very coarsely arranged. In such cases single cancer cells and groups of cells are observed in the tissues outside the apparent limit of the tumour. The reports of microscopists on these tumours are to the effect that they appear to be particularly malignant. I believe this opinion to be generally correct.

I will give one case in support of it, which I have already published elsewhere : *

I removed a portion of the right half of the tongue to an inch behind a flat plaque of epithelioma right on the border. Finding it a little thicker than had been expected, I cut out a lump of muscle in the floor of the mouth beneath the seat of the ulcer, but did not pretend to remove any muscles, or groups of muscles, to their insertions. The contents of the anterior triangle were removed two or three weeks later. The parts were examined by the

* *A System of Operative Surgery*, edited by Burghard. Oxford, 1909 ; vol. ii. p. 241

Imperial Cancer Research. Dr. Murray reported that no cancer was found in the glands, but that the primary lesion exhibited a very high degree of malignancy. Columns of cancer cells infiltrated the muscles far beyond the apparent limit of the disease. I examined the sections myself, and fully agreed with Dr. Murray's report. I was therefore very unhappy about the future of the patient, and wrote to Dr. Joseph Bryan and to Dr. Collins Warren, of the United States, begging them to keep the patient under observation, as I thought there would probably be recurrence in the muscles of the tongue. But there was not any.

Six months after the operation a lump was unexpectedly found on the *left* side of the neck. An attempt was made by an expert surgeon to remove the contents of the left anterior triangle, but extensive and fixed disease was discovered, and the patient succumbed to the attempt. The sequel of the case proved the correctness of Dr. Murray's report. There was early and extensive reappearance of the disease, but not where we expected to find it.

I can only assume that the glands provided better maintenance for the squamous cells than did the muscles of the tongue. I cannot believe that I did not leave some of these vigorous cells in the muscles of the tongue which were not removed. And cancer cells must, before the operation, have been conveyed

to the glands on the left side of the neck. The glands apparently suited them better than the muscles.

3. *When do Cancer Cells begin to Migrate?*

This question is the most important of the three. But, in endeavouring to answer it, we have to rely largely on conjecture and circumstantial evidence. Theoretically, there is no reason why the cells of any and every case of cancer should not begin to migrate from the first moment of their existence as independent creatures. But reasons have been given in the preceding paragraphs for believing that the cells of many cancers do not migrate so early. On the other hand, thousands of cases can easily be furnished to show that they migrate within a few months of the discovery of the tumour, cases in which the successful removal of the tumour has been followed by metastasis, either immediately or after a period which may be very considerable. And there are other cases which suggest that migration of the cells of some primary tumours commences at a very early period. I will give two cases in point:

An old gentleman had a very tiny ulcer of the front part of the floor of the mouth and a

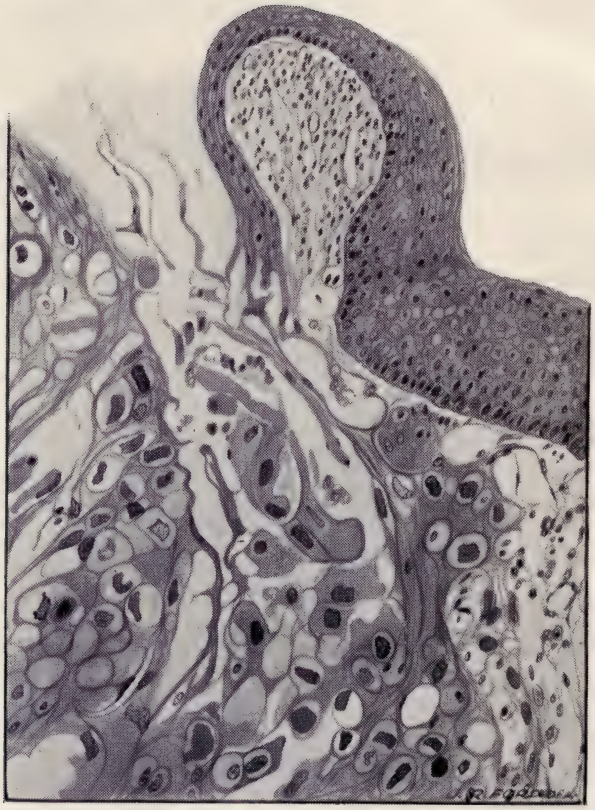

FIG. 18.—Squamous carcinoma of tongue.

number of large fixed glands under the floor of the mouth and in the neck. I cut out a fragment of the ulcer, had sections made of it, and found that it presented the characters of squamous carcinoma. The patient was very unobservant, but believed the little ulcer and the glands had appeared about the same time. The ulcer was so trivial that Dr. Mackenzie Davidson cured it with a single application of radium (the only case of buccal epithelioma which I have myself known to be cured by radium). We sent him to Paris to see whether radium could be successfully applied to his glands, but he died there in the course of a very short time.

The details of this case leave much to be desired. The second case is much more to the point:

In the spring of 1901 I removed by a trivial operation one of the smallest squamous carcinomas of the tongue that I have ever seen. It was just under the left border of the tongue in the middle of an old area of leucoma and glossitis, due to past syphilis (Fig. 18).* In

* A section of it is figured in the *Second Scientific Report of the Imperial Cancer Research Fund*, 1905, p. 45, Fig. 35; not because it was cut in their laboratory, but because, owing to its minute size, some microscopists at that time would not have accepted it as an undoubted squamous carcinoma, and on account of the subsequent history of the case.

October 1904, three and a half years after the operation on the tongue, he consulted me on account of a large, hard, glandular mass in the parotid (upper carotid) region on the same side. It had only been noticed three months. I removed it, and found it to be squamous carcinoma (Fig. 19). There was no disease in his throat, or cheek, or mouth, or tongue, for I had cut out the whole of the little area of leucoma and glossitis. And the whole operation had been so small that the doctor who first saw the tumour in the neck and examined the mouth, and particularly the tongue, for a possible primary lesion, did not perceive that an operation had been performed on the left border of the tongue.

The Resisting Power of the Host

It is quite evident that the resistance of the host plays a much more important part in relation to the prognosis and treatment of cancer than it has hitherto been supposed to do. Most of our knowledge regarding resistance is due to experimental investigation, and is quite newly acquired.* Amongst other things, we

* We are largely indebted to the Imperial Cancer Research for our information, and I would refer those who desire to make themselves acquainted with what has been done in relation to this matter to the Scientific Reports of the Fund.

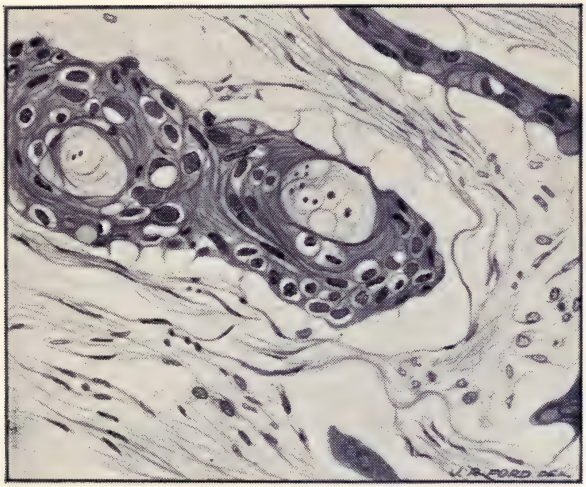

FIG. 19.—Glands removed more than three years after successful removal of the tiny tumour of the tongue.

have learnt that resistance lies more in the individual tissues than in the blood or fluids of the host. So far as animals are concerned, we have learnt that resistance is much greater in some animals than in other animals of the same species; that it is not always the same in strength; that it may be increased or diminished by certain definite measures; together with many other matters on which I need not dwell now.

Hitherto we have been in the habit of believing that the success of our operations has been consequent on the complete removal of the tumour, including every outlying cell and group of cells, and in the wide removal of glands which contain metastasis or in which metastasis may be expected. To this we have rightly added the removal of the tissues between the tumour and the glands for the cancers of certain parts of the body, such as the breast. In those cases in which the glands which are liable to metastasis have not been removed, and the result has nevertheless been successful, we have attributed success to the fortunate circumstance that the tumour was removed before the cancer cells had reached the glands. No doubt these assumptions are often correct. But I think there is equally no doubt that

migration has already commenced in other cases which are successful, and that success has been dependent on the resisting power of the tissues of the host. I do not know how otherwise to account for some of the conditions whicha re not of uncommon occurrence.

Take, as an example, the history of the case of spheroidal-cell carcinoma, represented in Figs. 12 and 13. The operation included the entire breast, the contents of the axilla, the tissues between the breast and the axilla, and a part, but not the whole, of the greater pectoral muscle. Five years later I removed a single recurrence, as large as a broad bean, from the muscular tissue below the scar, and perhaps 1½ inch from it. It was undoubtedly due to cancer cells which had not been removed at the operation. For the structure of the tumour and of the recurrent growth were identical. The cells seemed to have remained inactive for more than four years, and then to have grown and multiplied to form a small mass. The resistance of the host held them lethargic for several years. I cannot believe that this was the only group of cancer cells left at the operation. It is far more probable that it was one of several or many groups, which had escaped removal, but that it was the only one of them which succeeded later in overcom-

ing the resistance of the host. I know this patient was quite well five years after the second operation. From indirect information I have received I believe she is still quite well. I judge that her resisting power is still maintained. It may possibly have enabled her to destroy other groups of cells which might otherwise have developed into tumour masses.

Again, take the case of cancer of the tongue, which has been described, in which recurrence was expected in the muscle, but actually occurred in the glands of the opposite side of the neck. I do not believe that I removed every piece of muscle which contained cancer cells. Yet no mass grew from those that were left, and this I attribute to the resisting power of the muscles which lay at some distance from the primary disease.

The Value of Properly Designed and Executed Operations

It may be inferred from what has been said that I have much greater faith in the resistance of the host than I have in extensive operations, and that I attribute a great part of our success rather to good fortune than to skill. I hasten to correct this impression. If there be one

thing which is more clearly proved than another in relation to malignant disease in the course of the last thirty years, it is the wonderful improvement in the results of operations for cancer. Wide and early operations, adapted to the pathology of the particular variety of malignant disease in each particular part of the body, have been attended with very great success. Nor is this to be wondered at. For the tumour is the manufactory and the storehouse of cancerous cells. And even in those cases in which the cells have begun to migrate, it is most desirable to get rid of the chief source of cancer cells. The resistance of the host has a much better chance of contending successfully with scattered cells, perhaps not yet firmly established where they lie, after the removal of the tumour. Indeed, I have thought for a long time past that if a "specific" against cancer were discovered it might even then be very desirable to remove the primary lesion—the tumour.

It will be noted that, in connection with "wide and early operations," it is suggested that the operations must be "adapted to the pathology of the particular variety of malignant disease in each particular part of the body." For thirty years I have urged this. But it is

not yet by any means generally accepted or acted on. Because a particular scheme of operation is successful for a particular variety of cancer of one part of the body, a scheme as nearly like it as possible is recommended for a different variety of cancer in another part of the body. This method of reasoning by analogy has led to very serious errors in the scheme of operations. The operative treatment of cancer of the breast has been taken by a large number of surgeons as indicating the ideal which should be aimed at in operations for malignant disease of all parts of the body. It includes two very important features—the removal of the entire breast, and the removal in a continuous mass of all the tissues between the breast and the axillary glands. The success which has attended operations for cancer of the breast has led many persons to believe that precisely the same principles should be applied in every operation for cancer in which it is possible to apply them. Not many years ago there were distinguished surgeons who insisted that the entire tongue should be excised in every case of cancer of the tongue. For quite a number of years there were surgeons and laryngologists in the United States and on the Continent who removed the

entire larynx in every case of cancer of the larynx, whether intrinsic or extrinsic, whether large or small.

I think the "entire organ" craze has by this time died out, except for such organs as the breast, ovary, testis, etc. But the removal of the tumour, the associated glands, and the intervening tissues in one continuous mass still possesses great attraction for certain surgeons. It is recommended as a routine operation in cases of cancer of the tongue, in spite of the fact that it seriously adds to the danger of the operation and impairs the powers of speech and mastication. It is quite unjustified by careful observation and comparison of the results of operations. * I think I have recently seen it recommended for cancer of the lower lip, for I have seen some ghastly pictures of quite up-to-date operations on the lower lip. But I suppose they refer to very extensive primary diseases of the lip. I cannot conceive that any surgeon in his senses would make a routine practice of such horrible operations.

Some of these operations are recommended on the microscopical findings of some of the

* Burghard's *Operative Surgery*, Oxford, 1909; vol. ii., p. 247.

cases in which continuous sections have been cut from the tumour to the glands. Cancer cells have been found in the intervening tissues, and the conclusion has therefore been drawn that the intervening tissues ought to be removed in every case, in spite of the much greater danger to life from the operation and the much greater permanent crippling of the patient. Fortunately, this routine, which has been particularly urged in the treatment of cancer of the tongue, has not been adopted by the majority of surgeons.

The tumour of the tongue and the associated glands have been separately removed, and the results have been such as to justify separate removal as against continuous removal. These cases, and similar cases in other parts of the body, clearly show that every cancer cell or group of cells which the microscope discovers do not develop into tumours, even when they seem to have made good their footing in the tissues at some distance from the tumour. I have been so impressed with the danger of trusting implicitly to microscopic findings and planning operations on them, that I have ventured to lay down the axiom—"*that if an operation does not fulfil the requirements of pathology, and is nevertheless exceedingly suc-*

cessful, the pathology which relates to it must be revised: either the observations are incorrect, or the deductions which are drawn from them are not justified." *

* Burghard's *Operative Surgery*. Oxford, 1909; vol. ii., p. 241.

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